Shock & vasoactive medications

June 17, 2024 by **Josh Farkas**

CONTENTS

Initial approach to shock

- Introduction (#introduction)
- Diagnosis (#diagnosis)
- Causes of shock (#causes_of_shock)
- Evaluating the cause of shock (#evaluating_the_cause_of_shock)
- Initial stabilization (#stabilization)

Optimization & refractory shock

- Approach to hemodynamic optimization (#general_approach_to_hemodynamic_optimization)
- Approach to refractory shock (#approach_to_refractory_shock)

Vasopressors

- Rapid Pressor Reference 🚀 (#rapid_reference)
- Considerations when selecting a vasopressor (#considerations_when_selecting_a_vasopressor)
- Core agents:
    - Dobutamine & milrinone:

        - Selecting dobutamine and/or milrinone (#selecting_dobutamine_and_or_milrinone)
        - Milrinone dosing (#milrinone)
        - Dobutamine dosing (#dobutamine)
    - Isoproterenol (#isoproterenol)
    - Vasopressin (#vasopressin)
        - Vasopressin in septic shock (#vasoinsepsis)
    - Phenylephrine (#phenylephrine)
    - Norepinephrine (#norepinephrine)
    - Epinephrine (#epinephrine)
- Adjunctive agents:
    - Methylene blue (MB) (#methylene_blue_(MB))
    - Hydroxocobalamin (B12) (#hydroxocobalamin)
    - Angiotensin II (#angiotensin_II)
- Oral vasopressors:
    - Midodrine (#midodrine)
    - Droxidopa (#droxidopa)
    - Ephedrine (PO/IV) (#ephedrine)
- Other related topics:
    - Peripheral vasopressors (#peripheral_pressors)
    - Dopamine (#just_say_no_to_dopamine)
    - Fludrocortisone (#fludrocortisone)

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introduction

(back to contents) (#top)

Shock is a state of systemic hypoperfusion, with inadequate blood supply to the tissues. Unfortunately, this may occur in different ways. The most simple physiology of shock is cardiogenic shock, with low cardiac output to the entire body. However, septic shock can occur with an *elevated* cardiac output due to *micro*vascular dysfunction at the tissue level (blood shunts through some vessels, while ignoring others). Because shock has varying physiologies,

it defies any simple operational definition at the clinical level. Shock is a bit like obscenity – after a while, you know it when you see it.

Shock is extraordinarily important because it is generally a *final common pathway* before death. Most serious diseases are capable of causing shock. Left untreated, shock will progress to multi-organ failure and death. However, shock is often *reversible*, thereby avoiding death.

The importance of promptly diagnosing shock and discerning its cause cannot be overstated. Unfortunately, shock may present in a variety of ways, so diagnosis isn't always so simple. For example, shock is typically associated with *hypotension* and *reduced* cardiac output, but it can also occur with normal blood pressure and an *increased* cardiac output.

Different types of shock present differently. For example, the stereotypical patient with early sepsis and distributive shock will appear quite different from the patient with cardiogenic shock (table below). Unfortunately, reality isn't quite this simple. Advanced cardiogenic shock often causes bacterial translocation from the intestines, leading to systemic inflammation and vasodilation. Alternatively, advanced septic shock frequently causes a septic cardiomyopathy. Thus, advanced cardiogenic shock and advanced septic shock may be very difficult to sort out.

classic appearance of septic vs. cardiogenic shock

	Sepsis	Heart failure
Clinical appearance	- Generally look sick. - Often tachypneic, delirious, febrile ("toxic appearing")	- Often look deceptively normal. - May continue mentating, despite profoundly low cardiac output.
Skin examination	- Initially flushed, warm extremities. - Initially normal capillary refill (Later on may develop poor perfusion)	- Cool extremities - Poor capillary refill, may have mottling
Blood pressure	- Wide pulse pressure - Very low *diastolic* pressure	- Narrow pulse pressure - Both systolic and diastolic Bp are moderately reduced.
Urine output	Low	Low

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diagnosis

(back to contents) (#top)

There is no single diagnostic test for shock. Patients with various forms of shock will present differently. Nonetheless, there is a constellation of findings which often occurs in the context

of shock. As patients accrue many of these features, the possibility of shock should be seriously considered.

hemodynamics (trends > absolute values)

- **Hypotension** (e.g., MAP below ~65 mm, or significant drop from baseline).
- **Elevated shock index**:
  - Shock index = HR / SBP.
  - Shock index above ~0.8 suggests significant instability.
- **Bradycardia**: cardiac output is directly proportional to heart rate. Severe bradycardia (e.g. heart rate below ~45) should always raise concern for shock. Even if the blood pressure is maintained by compensatory systemic vasoconstriction, cardiac output and perfusion may still be poor (more on bradycardia here (https://emcrit.org/ibcc/bradycardia/#why_bradycardia_is_dangerous)).

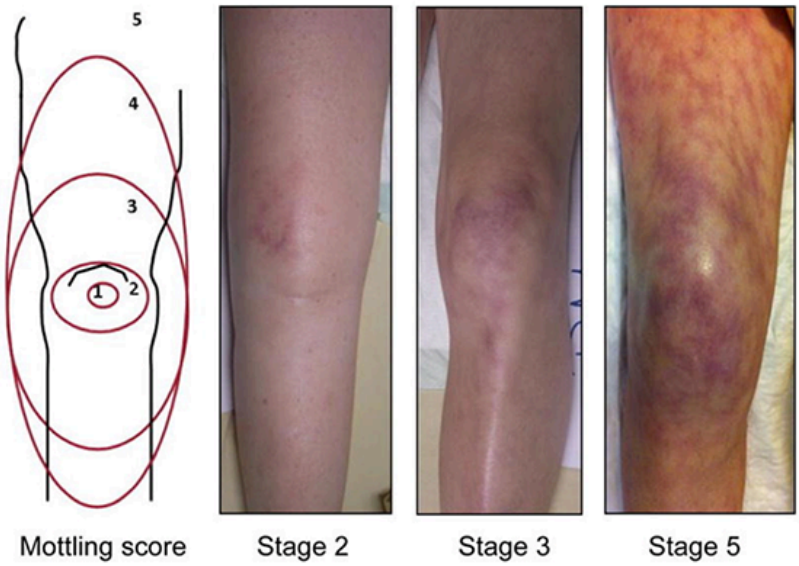
oliguria (or dark urine)

- Urine output below ~0.5 cc/kg/hour is worrisome for renal malperfusion.
- Dark urine also suggests renal hypoperfusion (e.g., immediately after Foley catheter insertion, before the urine output is known).
- (More on the approach to oliguria: 📖 (https://emcrit.org/ibcc/acute-kidney-injury/#approach_to_oliguria)).

skin perfusion

- **Cool hands and knees** are an early sign of vasoconstriction with reduced cardiac output. Normal people may have cool hands, but if *all* extremities are cool that's more specific for hypoperfusion.
- **Mottling** is less sensitive, but more specific for hypoperfusion and elevated mortality (figure below). Mottling suggests active endogenous vasoconstriction, implying that the patient would benefit from an increase in cardiac output (e.g. an inotrope) – not additional exogenous vasoconstrictors.
- **Capillary refill time**: The ideal technique may be to compress the fingertip using a slide with enough pressure to cause blanching for ten seconds. Any clear surface can also be used, such as a plastic urine specimen container.(27908340

(https://www.ncbi.nlm.nih.gov/pubmed/27908340)) Normal capillary refill time is <3-4 seconds, whereas >5 seconds suggests impaired perfusion.



Mottling isn't particularly sensitive, but when present it is highly concerning. (Image from Galbois A 2015 (http://www.sciencedirect.com/science/article/pii/S0168827814007417))

delirium

- New-onset delirium can be a sign of shock (especially *septic* shock). However, this is neither very sensitive nor specific.
  - Most new-onset delirium isn't due to shock.
  - ⚠️ Patients with acute-on-chronic cardiogenic shock can maintain normal mentation despite profoundly low cardiac output.

hyperlactatemia (or jumping anion gap)

- Lactate >4 mM suggests shock, but this has a broad differential diagnosis. Lactate usually doesn't reflect oxygen deficiency, but rather endogenous epinephrine in *response* to physiologic stress. 🌊 (https://emcrit.org/pulmcrit/understanding-lactate-in-sepsis-using-it-to-our-advantage/) This explains why lactate can be normal in shocked patients who have inadequate sympathetic nervous function.
  - High lactate level *is* worrisome. This should be interpreted to represent shock or some other impending disaster until proven otherwise.
  - Normal lactate isn't necessarily reassuring (it can occur in shock).

    - (Further discussion of the evaluation of hyperlactatemia: 📖 (https://emcrit.org/ibcc/agma/#evaluation_&_treatment_of_lactate_elevation))
- 💡 A sudden jump in the patient's anion gap suggests hyperlactatemia if there is no obvious alternative explanation (e.g., absence of starvation or diabetes that could cause ketoacidosis). In a hospitalized patient, a jumping anion gap represents shock until proven otherwise.
    - (Further discussion of the evaluation of anion gap elevation: 📖 (https://emcrit.org/ibcc/agma/#evaluation_of_anion_gap_elevation))

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causes of shock

(back to contents) (#top)

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arrhythmic shock

- Tachyarrhythmia (usually >>150 b/m).
- Bradyarrhythmia (usually <45 b/m).

hypovolemic shock

- Hemorrhage:
    - External bleeding (penetrating trauma, postpartum).
    - GI bleed.
    - Retroperitoneal bleed.
    - Intraperitoneal bleed.
    - Hemothorax.
- Hypovolemia:
    - Vomiting and/or diarrhea.
    - Over-diuresis.
    - Post-ATN or postobstructive polyuria.

LV failure ("cardiogenic" shock)

- LV systolic failure:

    - MI.
    - Progressive chronic cardiomyopathy.
    - Acute non-ischemic cardiomyopathy:
        - Peripartum.
        - Septic.
        - Stress-induced (Takotsubo).
        - Myocarditis.
    - Post-cardiotomy syndrome.
    - Overdose (e.g., beta-blocker).
- Acute aortic or mitral valve regurgitation:
    - Endocarditis.
    - Papillary muscle rupture.
    - Aortic dissection.
- Prosthetic valve thrombosis.
- Dynamic LV outflow tract obstruction (LVOTO).

RV failure

- Pulmonary embolism.
- Decompensated chronic pulmonary hypertension.
- Right ventricular myocardial infarction.
- Progressive chronic cardiomyopathy.
- Acute non-ischemic cardiomyopathy:
    - Septic.
    - Myocarditis.
- Post-cardiotomy syndrome.
- VSD (ventricular septal defect).

obstructive

- Tamponade.
- Tension pneumothorax.
- Elevated intrathoracic pressure:
    - Abdominal compartment syndrome.
    - AutoPEEP.

vasodilatory shock ("distributive" shock)

- Severe systemic inflammation:
  - Septic shock.
  - Pancreatitis.
  - Post-cardiac arrest SIRS.
  - Post-MI SIRS.
- Anaphylaxis.
- Endocrine:
  - Adrenal crisis.
  - Thyroid storm.
- Neurogenic shock:
  - Trauma.
  - Spinal anesthesia.
- Liver failure.
- Excess vasodilatory drugs.

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evaluating the cause of shock

(back to contents) (#top)

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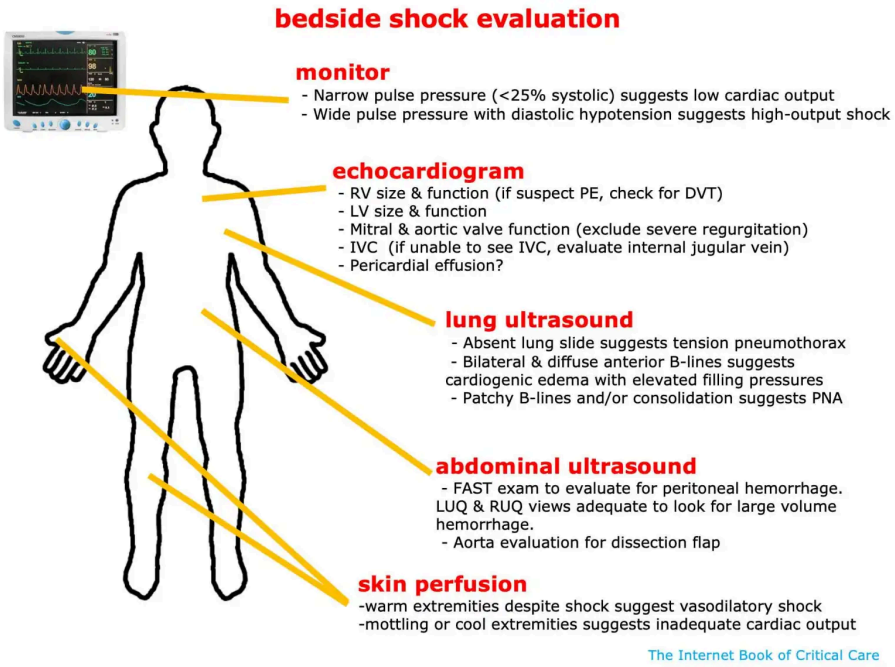
history and data review

- ? Cardiac history (Especially any prior information about cardiac structure/function such as EKG, echo, or even chest CT showing chamber size).
- ? Adrenal disease (Noting: Patients chronically on oral steroid may be assumed to be insufficient).
- ? History of venous thromboembolic disease.
- ? Immunosuppression, ? Invasive devices (e.g. hemodialysis catheters).
- ? Recent procedures or trauma.
- ? Current medications & *changes* in medication list.

examination



labs

- Electrolytes (including Ca/Mg/Phos).
- Complete blood count with differential.
- Coagulation studies.
- CRP (C-reactive protein).
- Lactate.
- If septic shock is suspected:
    - Blood cultures x2.
    - Urinalysis with reflex culture.
    - Sputum culture if clinically indicated.
    - Procalcitonin (if initiating antibiotics).
- Endocrine evaluation:
    - Random cortisol level (if adrenal insufficiency is possible).
    - TSH (if thyroid storm is suspected).
- Troponin (if ECG/history suggests acute MI).

radiologic studies

- ECG is occasionally helpful (e.g., may reveal occlusive MI, or RV strain).
- CXR (e.g., may reveal pneumonia or cardiogenic edema, implying LV failure).
- CT may be considered depending on the clinical scenario:

- CTA to evaluate for pulmonary embolism.
- CT abdomen/pelvis to evaluate for septic focus.

differential & categorization

Findings on ultrasonography and physical examination may be integrated as shown below. This tends to work best in previously healthy patients with a single mechanism of shock. Patients with multiple chronic problems or multifactorial shock may defy categorization.

bedside approach to undifferentiated shock/hypotension

	IVC or Jugular vein size	Lung POCUS	Significant pericardial effusion	RV dilation	LVEF	Mitral or aortic regurg?	Cardiac Output
Distributive shock - Septic shock - **Anaphylaxis*** - Adrenal crisis, Thyroid storm - Post-cardiac arrest SIRS - Pancreatitis, Hepatic failure - Neurogenic (trauma, spinal anesth) - Vasodilatory medications	↓↓ or normal	Normal (or focal abnormality from pneumonia)	-	-	nl / ↑	-	**High output:** - Warm extremities. - Low diastolic Bp. - Wide pulse pressure. - May be febrile. - May look toxic. - Capillary refill is variable.
Hypovolemic shock - Vomiting, diarrhea, overdiuresis - Hemorrhage (GI, peritoneal, RP) **Abdominal compartm. syndrome**	↓↓↓	Normal	-	-	nl / ↑	-	**Low output** - Cool extremities. - Diastolic Bp may be normal. - Narrow pulse pressure. - Delayed capillary refill.
RV failure - PE, - Decompensated chronic PH - RV myocardial infarction	↑↑	Normal	-	+	nl / ↑	-	
Tamponade	↑	Normal	+	-	nl / ↑	-	
Tension pneumothorax	↑	No slide on affected hemithorax	-	-	nl / ↑	-	
AutoPEEP / high airway pressure - Asthma > COPD > ARDS - Exacerbated by hypovolemia - Dx based on history, vent waves	nl/↑	Normal	-	+/-	nl / ↑	-	
LV failure - MI - Myocarditis, postpartum CM - Takotsubo cardiomyopathy - Beta-blocker overdose	nl/↑	B-lines everywhere	-	+/-	↓↓	+/-	
Valve dysfunction - Endocarditis - Post-MI papillary muscle rupture - Prosthetic valve dysfunction **LV outflow obstruction (LVOTO)** - Elderly with chronic HTN - HOCM or Takotsubo CM	nl/↑	B-lines everywhere	-	-	nl / ↑	+	

POCUS can generally diagnose RV failure, tamponade, LV failure, or valve dysfunction. Unfortunately, hypovolemic and distributive shock often look relatively unremarkable on POCUS (both may present with a collapsed IVC). Thus, additional clues about the cardiac output will often be needed to sort out these etiologies. Unfortunately, in the later stages of shock, these distinctions may tend to blend together. For example, low cardiac output may eventually lead to tissue damage that causes inflammation, causing vasodilation. Alternatively, prolonged septic shock often leads to a stress cardiomyopathy with a fall in cardiac output. Thus, archetypal distinctions are most accurate in sorting out patients who present relatively *early* in their disease course.

***Anaphylaxis** can kill within minutes, if suspected then start epinephrine *without* delay.

Adrenal crisis: If suspected, immediately start empiric steroid. Dexamethasone 6 mg may be useful since this doesn't interfere with performing an ACTH stimulation test later on.

Septic shock is the most common cause of shock in critically ill adults. If a reasonably through evaluation fails to reveal any obvious cause of the shock (e.g., cardiopulmonary POCUS is unremarkable and the history is nonspecific), septic shock is likely. When in doubt, treat empirically for sepsis.

The Internet Book of Critical Care, emcrit.org/IBCC/shock

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stabilization

Stabilization must start immediately, often before the cause of shock is known. The following are common interventions to consider.

volume resuscitation

- Fluid administration should be tailored to the individual patient's hemodynamic assessment.
- Fluid is often provided in boluses (e.g., 500 ml) with attention to patient response. The total amount of fluid administered should generally be limited to <1-2 liters in the absence of a history suggesting substantial total-body volume depletion (e.g., severe gastroenteritis with a colostomy).
- Fluid administration can be diagnostic and therapeutic in confusing situations where hypovolemia is suspected:
    - If fluid resuscitation alone resolves shock, this supports a diagnosis of hypovolemia.
    - If fluid resuscitation fails, this suggests an alternative diagnosis. This is especially true if fluid resuscitation results in adequate filling pressures (e.g., full IVC) *without* resolving the shock.

vasopressor administration

- Vasopressor administration should be started immediately if the blood pressure is inadequate (e.g., MAP<60 mm).
- Vasopressors may be administered via a peripheral vein.
    - Norepinephrine may be given peripherally with careful monitoring of the IV site for limited periods of time.
    - Phenylephrine or epinephrine have a lower risk of extravasation and may be safer to use in situations with less rigorous monitoring.🌊 (https://emcrit.org/pulmcrit/phenylephrine-epinephrine-central-access/)

antibiotics

- If sepsis is possible, cultures should be performed and empiric antibiotics should be started without delay.

- In patients with possible sepsis, you don't necessarily need to go extremely broad with the antibiotics. A single broad-spectrum agent may be reasonable (e.g., piperacillin-tazobactam).

steroids

- Indicated for patients whom you suspect have adrenal crisis, for example:
  - Patients with known adrenal insufficiency.
  - Patients taking chronic steroids who recently missed doses.
- When in doubt about adrenal insufficiency, a reasonable approach is to give 6 mg dexamethasone and check a cortisol level simultaneously. Dexamethasone doesn't interfere with the cortisol level, allowing you to perform an ACTH-stim test later on if indicated. (More on adrenal crisis 📖 (https://emcrit.org/ibcc/adrenal-crisis/#top))

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general approach to hemodynamic optimization

(back to contents) (#top)

The following describes a general strategy for hemodynamic profiling and optimization. Please note that more specific and directed approaches may be more appropriate for unusual forms of shock (e.g., severe valvular disease, LV outflow tract obstruction, isolated RV failure). (Rola 2025)

bedside evaluation

- **Monitor**:
  - Vital signs.
  - Rhythm strip with corresponding evaluation of pulse oximeter and/or A-line tracing.
  - Right heart catheter parameters (if available).
- **Traditional examination**:
  - Cool/warm extremities.
  - Capillary refill.
  - Mottling (often starts on the *knees*).
  - Peripheral edema.

- **POCUS examination, including**:
  - RV function.
  - LV function.
  - IVC (and, if dilated, femoral vein doppler).
  - Anterior lung ultrasound.

Based on this evaluation, six key dimensions can be evaluated:

[1/6] RV function

- Traditional examination:
  - JVP elevation.
  - In subacute/chronic decompensation: peripheral edema, weight gain.
- POCUS:
  - IVC dilation. 📖 (https://emcrit.org/ibcc/rv/#ivc)
  - Femoral vein pulsatility. 📖 (https://emcrit.org/ibcc/rv/#fem)
  - RV dilation; TAPSE. 📖 (https://emcrit.org/ibcc/rv/#echocardiography_in_RV_failure)
- Right heart catheter:
  - CVP elevation >12-15 mm. 📖 (https://emcrit.org/ibcc/rhc/#CVP_(central_venous_pressure))
  - PAPi <1-2. 📖 (https://emcrit.org/ibcc/rhc/#RV_function_indicies)

[2/6] Excessive LV preload

- Traditional examination: Dyspnea, hypoxemia, possibly rales.
- POCUS: Lung B-lines bilaterally & diffusely (sensitive only for *acute* elevations, however).
- Right heart catheter: Elevated PA diastolic and/or PCWP. 📖 (https://emcrit.org/ibcc/rhc/#wedge_pressure_(aka_PCWP))

[3/6] LV systolic function

- Monitor: Pulse pressure <25% SBP suggests reduced stroke volume.
- POCUS: LVEF.
- Right heart catheter: LV stroke volume index.

[4/6] Systemic arterial vascular tone

- Monitor: Low DBP suggests vasodilation.
- POCUS: LVEF >>70% suggests vasodilation, if seen.
- Right heart catheter: SVRi.

[5/6] Cardiac output/perfusion

- Right heart catheter: Cardiac index.
- Traditional examination:
  - UOP is reassuring (if adequate).
  - Warm extremities.
  - Capillary refill <3 seconds.
  - Absence of mottling.

[6/6] Heart rate & rhythm

- Evaluate for bradycardia, tachycardia, or inappropriately normal heart rate.
- Evaluate for non-perfused beats.

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approach to refractory shock

(back to contents) (#top)

Patients with refractory shock usually have a pre-identified etiology of their shock. Nonetheless, some degree of clinical re-evaluation is often useful:

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diagnostic tests to consider for patients failing to respond to therapy

- **Cardiac imaging**:
  - Repeat POCUS evaluation to characterize hemodynamics.
  - Formal echocardiography should be considered.
  - Review any available CT imaging of the heart. 📖 (https://emcrit.org/ibcc/cxr/)
  - Evaluate for unusual forms of shock (e.g., LVOTO 📖 (https://emcrit.org/ibcc/lvoto/)).
- **Laboratory evaluation may include**:

- ABG/VBG and electrolytes (to evaluate pH status).
- Glucose level.
- Ionized calcium level.
- Cortisol level.
- TSH & free T4 levels.
- Lactate level.
- Complete blood count (to evaluate for hemorrhage).
- Infectious evaluation (e.g., CRP, procalcitonin, blood cultures).

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treatment options include

Multimodal therapy is often required. Below are over a dozen potential treatments to consider:

define & optimize MAP targets

- **Central arterial line insertion** (femoral or axillary):
  - Radial arterial lines may underestimate blood pressure. (https://emcrit.org/pulmcrit/a-line/)
- **Reducing MAP target**:
  - If very high doses of norepinephrine are required to achieve a MAP >65 mm (e.g. >1 ug/kg/min), this may be causing more harm than good. Reducing the MAP target to >55 or >60 could potentially represent a more beneficial balance of vasopressor benefit vs harm.

review medications & stop drugs that cause hypotension

- **Hemodynamically stable analgosedation**:
  - Propofol or dexmedetomidine are excellent sedatives, but they can reduce blood pressure.
  - More hemodynamically stable agents may be preferable (e.g., ketamine infusion, PRN benzodiazepines).
- Discontinue any alpha-blockers being utilized for BPH (benign prostatic hypertrophy).

optimize preload

- **PEEP reduction**: Reducing the mean airway pressure may increase preload for patients on positive pressure ventilation.
- **autoPEEP**: Evaluate for this and manage aggressively.
- **Volume administration:** patients have usually been fluid resuscitated by this point, but preload and fluid status should be re-evaluated (e.g., with POCUS).

metabolic optimization

- **Temperature management**:
  - Hypothermia causes cardiac dysfunction.
  - Hyperthermia causes increased metabolic demands and reduced systemic vascular resistance.
- **Intravenous calcium**:
  - Consider this for patients with ionized calcium <0.8 – 0.9 mM.
  - (Further discussion of calcium infusions for refractory shock: 📖 (https://emcrit.org/ibcc/hypocalcemia/#intravenous_calcium_for_refractory_shock))
- **pH optimization**:
  - **Bicarbonate**: management of acidosis may improve vasopressor responsiveness.
  - **Ventilator management**: consider increasing tidal volume and respiratory rate (but avoid autoPEEP).
  - **Dialysis** may be required.
- **IV thiamine** (to empirically treat for beriberi; may improve lactate clearance).
- **Steroid** (may enhance vascular responsiveness to vasopressors; especially for patients with sepsis/SIRS). (38202178 (https://pubmed.ncbi.nlm.nih.gov/38202178/))
- **Thyroid hormone replacement** for decompensated hypothyroidism (which is well known to cause vasopressor-refractory shock). Patients with pressor-refractory shock due to decompensated hypothyroidism should probably be treated with T3 to achieve more rapid improvement.

vasopressor optimization

- **High-dose norepinephrine** (there is no maximal dose 🌊 (https://emcrit.org/pulmcrit/high-dose-vasopressor/)).
- **Vasopressin**: ⚡ (#vasopressin)
  - Consider a loading bolus in refractory shock.

    - 0.06 U/min is safe for refractory vasodilatory shock (with monitoring for digital ischemia & hypoperfusion).
    - 0.1 U/min has been used in post-cardiac surgery vasoplegia. (18305265 (https://pubmed.ncbi.nlm.nih.gov/18305265/))
- **Epinephrine**: ⚡ (#epinephrine)
    - Especially useful in patients with relative bradycardia or reduced systolic function.
    - When in doubt, an *epinephrine challenge* can be attempted (empirical evaluation of the response to 4 mcg/min of epinephrine; if a favorable response occurs, continue epinephrine and titrate to effect).
- **Methylene blue**: discussed below: ⚡ (#methylene_blue_(MB))
- **Hydroxocobalamin**: discussed below: ⚡ (#hydroxocobalamin)
- **Angiotensin II**: discussed below: ⚡ (#angiotensin_II)

heart rate optimization

- **For relative/absolute bradycardia (e.g., HR<90 b/m)**, may consider:
    - Positive chronotropic agents (e.g., **isoproterenol**).
    - Anticholinergic therapy:
        - **Atropine** 💉 (https://emcrit.org/ibcc/bradycardia/#atropine) may be more effective.
        - **Glycopyrrolate** 💉 (https://emcrit.org/ibcc/bradycardia/#glycopyrrolate) may cause fewer CNS side-effects (e.g., 0.1-0.2 mg IV q6hr).
- **For paced patients**:
    - Temporary transvenous pacemaker: titrate heart rate to 100-120 b/m to determine if this improves perfusion.
    - Permanent pacing: consult electrophysiology to increase heart rate.
    - ⚠️ Caution: if increasing the rate of the electrical pacemaker reduces the number of native beats that are conducted through the patient's native conduction system, this may *not* be beneficial.

right ventricular optimization

- **Inhaled epoprostenol** for patients with right ventricular dysfunction.
- (More on managing RV failure: 📖 (https://emcrit.org/ibcc/rv/))

antibiotics

- Antibiotics should be considered if septic shock is possible.

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rapid reference

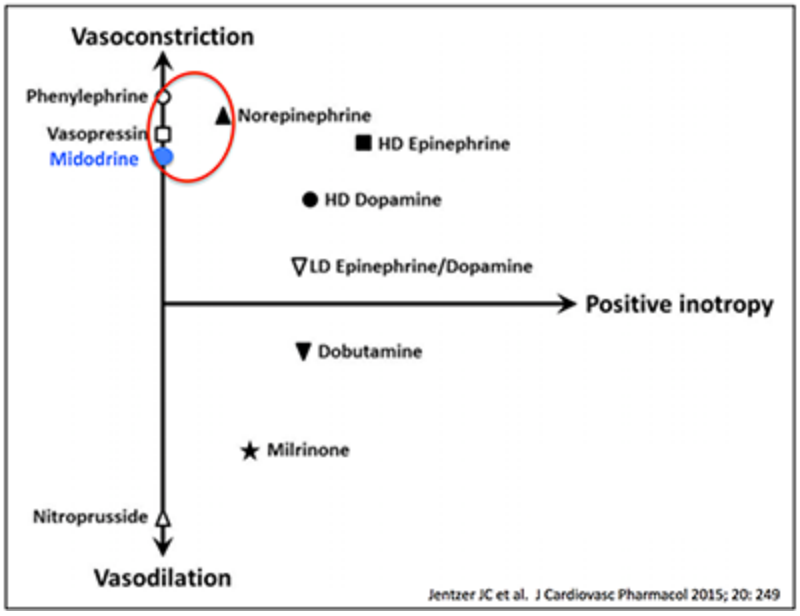
(back to contents) (#top)

Rough properties of various vasopressors

Drug Typical dose range	Target	Effect on - Heart rate - Inotropy - Ectopy	Effect on systemic vascular resistance	Effect on cardiac output	Effect on blood pressure	Effect on pulmonary vascular resistance	Main uses	Safe for peripheral use?
Inodilators								
Dobutamine 2-20 mcg/kg/min	αββββ	⇑⇑⇑	⇓	⇑⇑⇑	Variable	⇓	Cardiogenic shock	
Milrinone 0.375-0.75 mcg/kg/min	cAMP	⇑⇑⇑	⇓⇓	⇑⇑⇑	Variable	⇓⇓	Cardiogenic shock	
Isoproterenol 2-10 mcg/min	ββββ	⇑⇑⇑⇑⇑⇑	⇓	⇑⇑⇑	Variable		Bradycardia	Yes
Pure Vasopressors								
Vasopressin 0.01-0.06 U/min	V1 & V2	⇓	⇑⇑⇑	⇔/⇓	⇑⇑⇑	⇓	Distributive shock, Pulmonary HTN	No.
Phenylephrine 40-180 mcg/min	αααα	⇓	⇑⇑⇑	Variable	⇑⇑⇑	⇑⇑	Distributive shock	Yes
InoPressors								
Norepinephrine 0-40 mcg/min*	αααβ	⇑	⇑⇑⇑	⇔/⇑	⇑⇑	⇔	Shock (most types)	Yes, for short period with monitoring
Epinephrine 0-20 mcg/min*	αβββ	⇑⇑⇑	⇑	⇑⇑⇑	⇑⇑		Bradycardia, cardiogenic shock, sepsis, anaphylaxis	Yes
Dopamine, low 1-4 mcg/kg/min	Dopa-R	⇔	⇓	⇑	⇓		Zombie apocalypse (absence of better agents).	Probably not
Dopamine, medium 4-10 mcg/kg/min	αβββD	⇑	Variable	⇑⇑	Variable			
Dopamine, high 10-20 mcg/kg/min	αααβD	⇑⇑	⇑⇑	⇑	⇑⇑⇑	⇑		

*Listed ranges are typically used doses in the United States, but there is no true "maximal" dose. Some countries may tend to use higher doses than others. At very high doses, pressors may lose some receptor specificity. The best dose is the dose required to keep the patient alive – in some cases very high norepinephrine or epinephrine doses may be needed.

-The Internet Book of Critical Care, by @PulmCrit



considerations when selecting a vasopressor

(back to contents) (#top)

Options for vasopressor or inopressor include norepinephrine, epinephrine, phenylephrine, or vasopressin. Contrary to popular belief, there is no such thing as a "front-line" vasopressor. Different pressor agents might be ideal in different situations:

[1/4] peripheral access vs. midline/central access

- Vasopressin should probably be avoided in peripheral access.
- A proximal, well-functioning peripheral line may be used for any catecholamine vasopressor (norepinephrine, epinephrine, or phenylephrine).
- If peripheral access is very tenuous with a high risk of extravasation, epinephrine or phenylephrine might be the safest (these agents have the lowest risk of skin necrosis if extravasation occurs).

[2/4] heart rate & EF (reduced vs. normal vs. *hyperkinetic*)

- Inappropriately low heart rate and/or reduced EF might support:
  - Epinephrine.
  - Norepinephrine.

- Tachycardia, preserved/elevated EF, and pure vasodilatory shock might support:
  - Vasopressin.
  - Phenylephrine.
  - 💡 A markedly elevated EF is not beneficial, as this could increase the risk of subsequent cardiomyopathy and/or LV outflow tract obstruction. Such patients may benefit from an increase in afterload.

[3/4] is there hemodynamically significant RV failure?

- Phenylephrine is probably the *least* desirable in this situation.
- Norepinephrine might not be *ideal* (it's predominantly an alpha-agonist).
- Vasopressin may be a useful vasopressor (neutral effect on pulmonary vascular resistance).
- Epinephrine may be a useful inopressor (neutral effect on pulmonary vascular resistance; inotropic support for the right ventricle).

[4/4] when in doubt, choose norepinephrine

- If there is no compelling reason to choose an alternative agent, norepinephrine is a good default selection.

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selecting dobutamine and or milrinone

(back to contents) (#top)

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clinical use of inodilators

- ⚠️ Inodilators should be titrated against cardiac output or a surrogate of cardiac output (e.g., urine output). They *shouldn't* be titrated against blood pressure because they have no predictable effect on blood pressure (discussed above).
- Low-output cardiogenic shock.
  - These are most useful for patients with reduced cardiac output and *a high* systemic vascular resistance (SVR).

    - Care is required for patients with hypotension since there is a risk of exacerbating hypotension.
- Septic shock with inadequate cardiac output (as an add-on agent). However, if blood pressure is tenuous, *epinephrine* could be a superior choice.
- Right ventricular failure.
    - Both agents may help improve RV systolic function.
    - Milrinone may additionally reduce the PVR (pulmonary vascular resistance).

advantages of dobutamine

- [1] Easier titration, especially in renal failure (unlike milrinone, which may accumulate in renal failure, leading to hypotension). Dobutamine has a short half-life, making it easy to adjust the dose to determine its effect. In contrast, milrinone takes a long time to reach steady-state levels, so it's impossible to see the immediate impact of titrating it.
- [2] Prolonged dobutamine infusion may cause beta-receptor desensitization and reduced efficacy (tachyphylaxis). This may emerge over two or three days. (7405947 (https://pubmed.ncbi.nlm.nih.gov/7405947/)) Tachyphylaxis may be a problem, but it can also help wean the patient off dobutamine once the infusion runs for a long time (it may be easier to wean off than expected).
- [3] Less likely to cause hypotension than milrinone.

advantages of milrinone

- [1] More significant pulmonary vasodilation (beneficial in RV failure). (3687783 (https://pubmed.ncbi.nlm.nih.gov/3687783/))
- [2] Milrinone combines better with epinephrine (whereas dobutamine plus epinephrine is redundant, as discussed further in the section on epinephrine).
- [3] Milrinone may work better in patients who have just received a beta-blocker, especially nonselective beta-blockers (milrinone bypasses the beta-receptor).
- [4] Less arrhythmogenic & chronotropic effect than dobutamine.
    - Milrinone may increase myocardial oxygen demand *less* than dobutamine.

milrinone + {dobutamine/epinephrine}

- Milrinone may be combined with a catecholamine inotrope (e.g., dobutamine or epinephrine).
- Milrinone and dobutamine likely have additive effects in terms of increasing stroke volume and reducing left ventricular end-diastolic pressure (LVEDP). (3731427 (https://pubmed.ncbi.nlm.nih.gov/3731427/))
- Milrinone and epinephrine are another useful combination; this is discussed further in the section on epinephrine. ⚡ (#epinephrine)

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milrinone

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- Hypotension or normotension with a high vasopressor requirement.
- Severe aortic stenosis.
- Arrhythmias.
- Renal failure.

drug-drug interactions

- Soluble guanylate cyclase stimulators (riociguat, vericiguat) may cause additive hypotension.
- Cilostazol (synergistic phosphodiesterase inhibition).

side effects

- Hypotension.
- Arrhythmias (atrial and/or ventricular).
- Exacerbation of myocardial ischemia.
- Thrombocytopenia (reversible decrease in platelet count, especially with prolonged use).

---

indications, advantages 👍

- Selection of milrinone vs. dobutamine is discussed above: ⚡ (#selecting_dobutamine_and_or_milrinone)

---

dosing

milrinone dosing

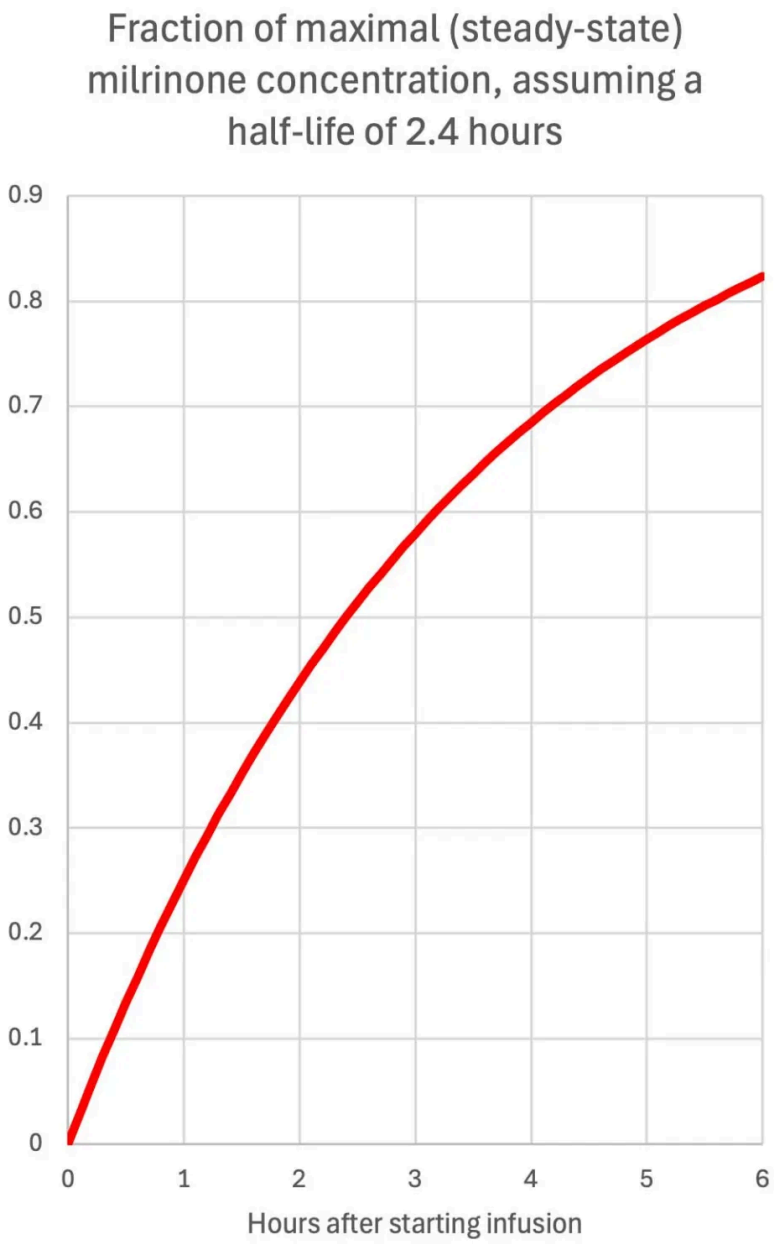
- The standard dose range is 0.25-0.75 ug/kg/min, but lower doses are often used in clinical practice (0.125-0.37 ug/kg/min). (Irwin & Rippe 9e)
- Doses >0.5 ug/kg/min often cause problematic hypotension. (32281470 (https://pubmed.ncbi.nlm.nih.gov/32281470/))
- Titration should occur at intervals of >2-4 hours to accommodate the long half-life. (Brown 2023)
- ⚠️ Be cautious in renal failure, which may cause milrinone accumulation and subsequent hypotension. (38613381 (https://pubmed.ncbi.nlm.nih.gov/38613381/))
- ⚠️ Milrinone will often drop the blood pressure, which may require up-titration or the addition of a vasopressor (usually norepinephrine). Make sure you have room to escalate norepinephrine and/or vasopressin if needed.

milrinone bolus?

- This should only be done *selectively* in patients who are most likely to respond, and with intense monitoring. The primary concern is provoking *hypotension*, so the best candidate for a milrinone bolus would be a patient with baseline *hypertension*.
- Consider a loading dose of 25-50 mcg/kg infused over 10 minutes. If a 25 ug/kg loading dose doesn't result in an adequate response, a second bolus of 25 ug/kg may be given. (Brown 2023)
- Using a loading dose may clarify the effect of milrinone on the patient's pharmacokinetics. The hemodynamic effects may peak 5-10 minutes after receiving the bolus, so careful monitoring is required throughout this period (Gutierrez 2024). There is a risk that the milrinone bolus will cause hypotension. Nonetheless, the advantage of

bolusing is that blood pressure can be carefully monitored during the period of maximal vulnerability (as opposed to initiating an infusion and experiencing hypotension several hours later).

LIAT (loading infusion auto-titration) strategy



- This is a strategy for rapidly and safely achieving a therapeutic milrinone infusion. It represents a compromise between giving a bolus versus starting a low-dose milrinone infusion at an arbitrary dose.
- [#1] A *loading infusion* is initiated at the upper end of the dosing range (e.g., 0.75 ug/kg/min). This will cause milrinone levels to rise in a *steady* and *controlled* fashion (as

shown in the graph above). Although the infusion is continued at a fixed rate, milrinone levels will accumulate, causing the drug to *auto-titrate* itself.

- [#2] Hemodynamics are meticulously monitored to determine when a therapeutic effect is achieved (e.g., with a pulmonary artery catheter).
- [#3] As soon as a satisfactory effect is seen, the *loading infusion* is stopped, and the patient is transitioned to a lower dose *maintenance infusion*. The rate of the maintenance infusion can be *calculated* based on how *long* it takes to reach a therapeutic effect using the following equation: (https://emcrit.org/pulmcrit/loading-infusion-auto-titration/)

$$(Optimal\ maintence\ infusion\ rate) = (Loading\ infusion\ rate)\left[1 - e^{\frac{-0.693(infusion\ time)}{half-life}}\right]$$

---

pharmacology

- **Absorption**: IV administration.
- **Distribution**:
  - Protein binding ~70% (mostly to albumin).
  - Vd 0.38 L/kg (bolus).
  - Vd 0.45 L/kg (infusion).
- **Metabolism**:
  - Limited hepatic metabolism (~10% may undergo glucuronidation to an inactive metabolite).
- **Elimination**:
  - Renal elimination as unchanged drug (~85%).
  - Active tubular secretion (renal clearance exceeds glomerular filtration rate).
- **Half-life & duration of action**:
  - The half-life is ~2.5 hours in normal renal function. Consequently, without a loading bolus, it may take ~6 hours to reach steady state.
  - Half-life is prolonged in renal dysfunction.

mechanism

- Milrinone is a selective inhibitor of phosphodiesterase type-3, thereby increasing intracellular cyclic AMP levels within the myocardium and vascular smooth muscle.
- Drugs with a similar mechanism of action:
  - Theophyline is a nonselective inhibitor of all five types of phosphodiesterase.
  - Glucagon activates a Gs protein, which stimulates adenylate cyclase to generate cAMP.

physiological effects

- Milrinone functions predominantly as a vasodilator (including venodilation, systemic arterial vasodilation, and pulmonary arterial vasodilation). Increased cardiac output is primarily driven by reduced systemic vascular resistance (with less effect on inotropy).
- Blood pressure effects are somewhat unpredictable (similar to dobutamine), but milrinone may be more likely than dobutamine to cause *hypotension*.

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dobutamine

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- Hypotension.
- Arrhythmias.
- Dynamic LV outflow tract obstruction (LVOTO).
- Sulfite sensitivity (sometimes occurs in asthma).
- Congenital prolonged QT syndrome (may cause torsade in some forms of congenital prolonged QT syndrome).

drug-drug interactions

- MAO-I (monoamine oxidase inhibitors) may increase the dobutamine concentration (e.g., linezolid, phenelzine, selegiline, tranylcypromine).
- COMT inhibitors (entacapone, opicapone, and tolcapone).

side effects

- Hypotension (or, less frequently, hypertension can occur due to a robust increase in cardiac output).
- Arrhythmias (atrial and/or ventricular arrhythmias).
- Myocardial ischemia may be worsened.
- Hypersensitivity reactions (e.g., rash, fever, eosinophilia, bronchospasm) have been reported, possibly related to a sodium metabisulfite component.

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indications, advantages 👍

- Indication & selection of inodilators is discussed above: ⚡ (#selecting_dobutamine_and_or_milrinone)

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dosing

- A starting dose is often 2.5-5 ug/kg/min.
- 0-10 ug/kg/min might be a rough inotropic dose range.
  - Doses >10 ug/kg/min may worsen tachycardia without increasing cardiac output. (32281470 (https://pubmed.ncbi.nlm.nih.gov/32281470/))
  - Doses >10-15 µg/kg/min may cause more pronounced alpha-agonist vasoconstriction. (Gutierrez 2024)
- Most books and articles list a dose range of 2.5-20 ug/kg/min. However, it's dubious whether administering doses greater than 10-15 µg/kg/min is productive.

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pharmacology

- **Absorption**:
  - IV administration.
  - Effects begin within 1-2 minutes and reach their peak effect ~10 minutes later.
- **Distribution**:
  - Vd is ~0.2 L/kg.
- **Metabolism**:
  - Primary pathway: Metabolized in the liver and other tissues by COMT (catechol-O-methyltransferase) methylation to an inactive metabolite.
  - Secondary pathway: glucuronide conjugation.
  - Metabolism isn't affected by renal or hepatic dysfunction.
- **Elimination**:
  - Inactive metabolites are excreted in the urine.
- **Half-life & duration of action**:
  - Half-life is ~2 minutes.
- **Tachyphylaxis**: Cardiovascular effects at 72 and 96 hours are 66% and 57% those after two hours. (38792934 (https://pubmed.ncbi.nlm.nih.gov/38792934/))

mechanism

- Dobutamine mainly stimulates beta-1 receptors > beta-2 receptors, with a little stimulation of alpha-1 receptors.

physiological effects

- Dobutamine primarily increases cardiac output by enhancing contractility, with a relatively modest increase in heart rate. Dobutamine does cause some systemic vasodilation as well. (Brown 2023)
- Stroke volume:
  - Increases with low doses of dobutamine (e.g., 2.5 mcg/kg/min). With continued dose escalation, stroke volume may not increase further. (38792934 (https://pubmed.ncbi.nlm.nih.gov/38792934/))
  - In *septic shock*, inotropic effects may be blunted (such that effects on cardiac output are largely due to increases in heart rate). (38792934 (https://pubmed.ncbi.nlm.nih.gov/38792934/))
- Heart rate:

    - Dobutamine has a mild positive chronotropic effect.
    - Rarely, if dobutamine causes a dramatic improvement in ejection fraction, this may decrease the endogenous sympathetic tone, resulting in a paradoxical decrease in heart rate. (Brown 2023)
- Systemic vascular resistance:
    - G*enerally reduced* due to beta-2 agonist stimulation and also reduced endogenous sympathetic tone in response to improved cardiac output.
    - However, dobutamine can also stimulate alpha-1 receptors, which may counterbalance this, leading to relatively little change in systemic vascular resistance. (Irwin & Rippe 9e)
- Blood pressure:
    - The effect is unpredictable, as it depends on the myocardium's responsiveness to an inotropic challenge.
    - If inotropic stimulation increases stroke volume and heart rate, blood pressure may remain stable.
    - If the heart *canno*t increase its stroke volume, the vasodilator effect may predominate, leading to a drop in blood pressure.
- Microcirculatory effects:
    - Dobutamine may improve microcirculatory perfusion independent of systemic macrohemodynamics. (38792934 (https://pubmed.ncbi.nlm.nih.gov/38792934/))

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isoproterenol

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications (all relative)

- Active myocardial ischemia (may worsen).
- Heart block due to digoxin toxicity (higher risk of proarrhythmia).

drug-drug interactions

- COMT inhibitors (e.g., entacapone, opicapone, and tolcapone).

side effects

- Cardiovascular:
  - Tachycardia.
  - Arrhythmias.
  - Exacerbation of myocardial ischemia.
  - Hypotension could occur (beta stimulation may cause peripheral vasodilation, so if the heart rate doesn't increase appropriately, unopposed vasodilation could drop the BP).
- Complications of beta-2 stimulation:
  - Hyperglycemia.
  - Hypokalemia.
  - Hyperlactatemia.
  - Diaphoresis.
  - Tremor.

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indications, advantages 👍

- **Primary indications**:
  - **Bradycardia**: Isoproterenol is probably the most potent chronotrope. It may be effective in patients who are refractory to epinephrine. This might be explained by the fact that epinephrine causes vasoconstriction and tachycardia, triggering a reflex bradycardia due to a baroreceptor effect.
  - **Torsade de Pointes**: Isoproterenol is often used to increase heart rate and thus avoid pause-dependent torsade in patients with torsade due to medication- or electrolyte-induced QT prolongation.
- **Potential/theoretical uses**:
  - **Right ventricular failure with elevated PVR**: Isoproterenol's beta-2 agonist activity (without any counterbalancing alpha-agonist activity) will tend to *reduce* pulmonary vascular resistance. This *theoretically* might allow isoproterenol to function as a

rapidly titratable, RV-friendly inodilator. However, the use of isoproterenol here is generally limited by tachycardia. (Bojar 2021)

- **Severe first-degree AV block?** PR interval >300 ms may cause a loss of atrioventricular synchrony. Isoproterenol accelerates AV nodal conduction, theoretically improving hemodynamics.
- **Bronchodilation**: Theoretically, it would exert similar effects to epinephrine.
- **Sketchy peripheral access**: Isoproterenol doesn't cause vasoconstriction, so giving it peripherally is safe.

---

dosing

- Usual dosing range is 1-10 ug/min.
- Some sources indicate that you may up-titrate as high as 20 ug/min. (Paw and Shulman 2025, Wellington 3e)
- Titrate against heart rate.

---

pharmacology

- **Absorption**: IV administration.
- **Distribution**:
  - Rapidly distributes throughout the extracellular fluid compartment.
  - Highly water-soluble.
  - Protein binding is 70%, primarily to albumin.
  - Doesn't appear to penetrate the blood-brain barrier (due to hydrophilicity).
- **Metabolism**:
  - Metabolized primarily by COMT (catechol-O-methyltransferase) in the liver and other tissues.
  - A minimally significant pathway is metabolism via MAO (monoamine oxidase). Unlike dopamine, norepinephrine, and epinephrine, isoproterenol is a *poor* substrate for MAO.
- **Elimination**:

    - Inactive metabolites are excreted in the urine.
- **Half-life & duration of action**:
    - Half-life is very short (2.5-5 minutes).

mechanism

- Isoproterenol is a pure, nonselective beta-agonist (it hits both beta-1 and beta-2 receptors).

physiological effects

- Isoproterenol functions predominantly as a highly potent *chronotrope*. Isoproterenol is also a positive inotrope (but compared to dobutamine, isoproterenol works primarily as a chronotrope, whereas dobutamine has a greater effect on stroke volume). (Gutierrez 2024)
- Beta-2 agonist activity:
    - It makes isoproterenol a more powerful chronotrope.
    - Reduces the pulmonary vascular resistance.
    - Causes metabolic side effects similar to epinephrine (lactic acidosis, hyperglycemia).

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vasopressin

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- Systemic hypoperfusion (e.g., mottling, cool extremities).
- Vascular disease, for example:
    - Mesenteric ischemia.
    - Limb ischemia.

    - Severe peripheral vascular disease.
    - Coronary artery disease.
- Poor IV access (relatively higher risk of skin necrosis in extravasation).

drug-drug interactions

- No pharmacokinetic drug-drug interactions.

side effects

- **Ischemic complications**, including:
    - Digital ischemia: Digital ischemia is unlikely to result from low-dose vasopressin alone but may be caused by a combination of vasopressin plus additional vasoconstrictor (especially norepinephrine). Especially for patients on high-dose vasopressin (0.08-0.1 U/min), follow capillary refill and consider down-titration or discontinuation if peripheral perfusion is not maintained.
    - Mesenteric ischemia.
    - Myocardial infarction.
- **Hemodynamic complications**:
    - Reduced cardiac output in selected patients: The physiology here is largely *the same as with phenylephrine* (with the difference that vasopressin will be superior in RV failure). The effect of pure vasoconstrictors on cardiac output is discussed further below in the section on *phenylephrine drawbacks*. ⚡ (#phenylephrine)
    - Bradycardia.
- Skin necrosis following extravasation: If vasopressin extravasates, there is no ability to reverse its local vasoconstriction effects (unlike alpha-adrenergic agents, wherein extravasation can be treated with phentolamine). Extravasation of vasopressin can cause skin necrosis. Although high-quality data are lacking, peripheral vasopressin administration should probably be avoided if possible.
- Hyponatremia due to free water retention. This occurs only occasionally and is generally not a significant problem. RCTs have not detected this, but it does occur occasionally (you can tell the hyponatremia is due to vasopressin because when vasopressin is stopped, the patient will have a brisk water diuresis with increasing sodium levels).

---

indications, advantages 👍

clinical use of vasopressin

- **Septic shock**: discussed in the section below.
- **Post-cardiac surgery vasoplegia**: The VANCS trial demonstrated the superiority of vasopressin over norepinephrine.
- **Hepatorenal syndrome** (HRS).
- **Right ventricular failure**: Vasopressin may be used as a vasopressor agent that doesn't increase pulmonary vascular resistance.
- **Central diabetes insipidus**: only very low doses are needed (e.g., 0.01 units/minute or less).
- **Variceal gastrointestinal hemorrhage:**
  - Theoretically, vasopressin is a good choice because it causes splanchnic vasoconstriction.
  - In practice, vasopressin generally isn't helpful because BP is often very labile in these patients, so it's impossible to titrate vasopressin rapidly enough to keep up with hemodynamic swings.

---

indications & contraindications: vasopressin in septic shock

The role of vasopressin in septic shock remains controversial. As with all therapies, this should be tailored to each patient's hemodynamic profile (considering the pros versus cons of using vasopressin for every patient).

pros: *relative indications* for using vasopressin in septic shock

- [1] Refractory vasoplegic shock:
  - The exam shows warm extremities, elevated cardiac output, and low SVR.
  - LV systolic function is hyperkinetic.
  - Diastolic BP is low.
  - Hypotension persists despite a moderate dose of norepinephrine (>0.25-0.5 mcg/kg/min).

- [2] Tachyarrhythmias:
  - RCTs show that vasopressin reduces arrhythmias by 2.8% (especially atrial fibrillation). (31062052 (https://pubmed.ncbi.nlm.nih.gov/31062052/))
  - Vasopressin may be useful for patients with uncontrolled supraventricular tachyarrhythmias (e.g., AF with RVR) or recurrent ventricular tachyarrhythmias.
- [3] RV failure:
  - Vasopressin may induce systemic vasoconstriction without elevating pulmonary vascular resistance.

cons: *relative contraindications* for using vasopressin in septic shock

- [1] Poor systemic perfusion: (e.g., poor capillary refill).
  - Vasopressin has been shown in RCTs to increase the rate of digital ischemia.
  - If a patient has poor peripheral perfusion, vasopressin is unlikely to improve this and may worsen the situation. However, the effects of vasopressin on microcirculation are complex and not entirely known. (40731360 (https://pubmed.ncbi.nlm.nih.gov/40731360/))
- [2] Bradycardia:
  - Vasopressin increases BP and spares norepinephrine, which may worsen bradycardia.
  - For patients with bradycardia and hypotension or hypoperfusion, consider an inotrope.
- [3] Left ventricular systolic failure:
  - Vasopressin increases afterload, potentially worsening LV failure.
- [4] Absence of stroke volume variation:
  - Higher stroke volume variation was associated with vasopressin responsiveness in one study. (37480126 (https://pubmed.ncbi.nlm.nih.gov/37480126/))
  - Absence of stroke volume variation is a *pathological* finding that suggests cardiac dysfunction (either absolute or relative). Absence of stroke volume variation suggests that the heart may be unable to handle increased preload and afterload induced by vasopressin (due to venoconstriction and arterial vasoconstriction, respectively).
- [5] Poor IV access:

- Vasopressin may have an increased risk of skin necrosis with extravasation (as compared to catecholamine vasopressors).

vasopressin challenge

- If a decision is made to trial vasopressin, the best approach may be a *vasopressin challenge*.
- (This is discussed further below in the section on *vasopressin dosing*.)

evidentiary basis for vasopressin in septic shock

- About one-third of patients with septic shock may have a relative vasopressin deficiency. (40731360 (https://pubmed.ncbi.nlm.nih.gov/40731360/))
- An individual patient data meta-analysis of RCTs in septic shock revealed the following effects of vasopressin: (31062052 (https://pubmed.ncbi.nlm.nih.gov/31062052/))
  - No effect on mortality (RR 0.98).
  - Vasopressin increased the risk of digital ischemia by 1.7%.
    - ⚠️ Monitor extremity perfusion and stop vasopressin immediately if digital ischemia occurs (e.g., fingertips are turning blue).
  - Vasopressin reduced the risk of arrhythmia by 2.8%.
  - There is no difference in mesenteric or coronary ischemia.
  - Vasopressin reduced the risk of dialysis, but this finding wasn't robust to sensitivity analyses.
- Numerous other meta-analyses have been published recently, yielding conflicting conclusions. The individual-patient-data meta-analysis of RCTs discussed above is arguably the highest-quality data. (31062052 (https://pubmed.ncbi.nlm.nih.gov/31062052/))
- **Vasopressin & mortality in septic shock?**
  - Several RCTs have been conducted on vasopressin, none of which have shown an impact on mortality.
  - The OPTIPRESS trial found that when vasopressin was initiated early, targeting a higher MAP goal increased mortality. (40358717 (https://pubmed.ncbi.nlm.nih.gov/40358717/)) This is an important danger signal that excessive vasoconstriction due to the combination of vasopressin plus norepinephrine may cause harm. Previous trials that used less vasopressin did *not* detect a mortality signal when targeting higher MAP goals.

- Over the past several years, several *retrospective correlational* studies have been published, suggesting that vasopressin dramatically reduces mortality. (34582425 (https://pubmed.ncbi.nlm.nih.gov/34582425/)) These results almost certainly reflect *confounding* (early vasopressin utilization may reflect a more aggressive sepsis management strategy overall). The phenomenon of time-to-intervention trials showing false-positive results is discussed further here (https://emcrit.org/pulmcrit/the-fallacy-of-time-to-intervention-studies/). If early vasopressin improved mortality, the VANISH or VANCS II trials should have been positive (these studies literally investigated front-line vasopressin).
- Evidence-based clinicians should base vasopressin therapy on the *numerous* available multicenter randomized controlled trials, rather than retrospective correlational studies. Available RCTs show either no mortality benefit or signals of potential harm from excessive vasoconstriction. (31062052 (https://pubmed.ncbi.nlm.nih.gov/31062052/), 40358717 (https://pubmed.ncbi.nlm.nih.gov/40358717/))

⚠️ vasopressin and peripheral perfusion

- Vasopressin has long been known to reduce digital perfusion and potentially provoke frank digital ischemia (e.g., meta-analysis of RCT-level evidence discussed above). Vasopressin *generally* reduces peripheral perfusion due to vasoconstriction. (18410861 (https://pubmed.ncbi.nlm.nih.gov/18410861/)) However, if vasopressin administration allows for a dramatic *reduction* in norepinephrine dosing, it can *improve* perfusion. (29319721 (https://pubmed.ncbi.nlm.nih.gov/29319721/))
- As we move towards a resuscitative strategy focused on microcirculation and peripheral perfusion, vasopressin may become less helpful. Honestly, one of the benefits of a perfusion-based strategy may be that it forces us to rethink the broad utilization of vasopressin in septic shock.
- Hernandez et al. (of the ANDROMEDA-SHOCK group) found that in the presence of vasopressin, a norepinephrine challenge was less likely to improve capillary refill. (38558268 (https://pubmed.ncbi.nlm.nih.gov/38558268/)) This interaction should be carefully considered when we fail to achieve microcirculatory endpoints (especially when contemplating whether to attempt a norepinephrine challenge).

- For patients on vasopressin who are not meeting peripheral perfusion targets, it will need to be carefully considered whether vasopressin is helping or harming them.

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dosing

dosing & titration of a vasopressin infusion

- **Cautions**:
  - ⚠️ The half-life of vasopressin is ~15-20 minutes. This is much longer than most vasopressors, which must be carefully considered when initiating or titrating vasopressin. Don't expect vasopressin to have an immediate effect without a loading dose. An infusion without a loading dose may take ~30 minutes to take effect.
  - ⚠️ Vasopressin shouldn't generally be given peripherally (if it extravasates, there is no antidote). (12163813 (https://pubmed.ncbi.nlm.nih.gov/12163813/))
  - ⚠️ Vasopressin can cause digital ischemia, especially when combined with norepinephrine. Pay careful attention to the perfusion of hands and feet; shut off vasopressin at the first sign of ischemic digits.
- **Septic shock**:
  - The usual dosing is 0.03-0.04 U/min (1.8-2.4 U/hour).
  - In refractory septic shock, vasopressin may cautiously be up-titrated to 0.06 U/min (3.6 U/hr). (VANISH trial, VANCS II trial, 37510705 (https://pubmed.ncbi.nlm.nih.gov/37510705/), 41222655 (https://pubmed.ncbi.nlm.nih.gov/41222655/))
- **Post-cardiotomy vasoplegic shock**:
  - May use a dose of up to 0.1 U/min (6 U/hr).

🔥 loading dose (vasopressin challenge test) 🔥

- Advantages of a vasopressin challenge test:
  - Immediate hemodynamic improvement in a critically unwell patient (without a loading dose, vasopressin takes 20-40 minutes to work).
  - Reveal the physiological response to vasopressin.

- How to perform a vasopressin challenge test: Load with 1U IV vasopressin, followed by 0.04 IU/min infusion. The 1U bolus will achieve a drug level equivalent to an infusion of ~0.04 U/min. (39685830 (https://pubmed.ncbi.nlm.nih.gov/39685830/))
- How to evaluate response to the vasopressin challenge:
  - [1] The VALOR study found that vasopressin-responsive patients generally experienced an increase in MAP by >18-22 mm following a 1-unit loading dose. Patients who failed to respond to the 1-U loading dose were more likely to develop digital ischemia following vasopressin infusion. (37480126 (https://pubmed.ncbi.nlm.nih.gov/37480126/))
  - [2] Follow peripheral perfusion closely to ensure there is no deterioration.
- (Higher loading doses have been suggested as well for various other situations.)
  - A 2 U loading dose will achieve an equilibrium level roughly equivalent to an infusion of 0.1 U/min (based on a half-life of 15 minutes). This may be administered in two 1-U doses separated by ~5 minutes. (32173168 (https://pubmed.ncbi.nlm.nih.gov/32173168/))
  - A 4-unit bolus has been recommended by some authors for the management of refractory hemorrhagic shock. (38613381 (https://pubmed.ncbi.nlm.nih.gov/38613381/)) This is quite aggressive but could be reasonable in a peri-code situation.

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pharmacology

- **Absorption**: IV administration.
- **Distribution**:
  - Distributed into the extracellular fluid compartment (Vd ~0.2 L/kg).
  - Circulates mostly unbound to protein.
- **Metabolism**:
  - Vasopressin is a peptide hormone. It is metabolized by tissue peptidases mostly in the liver and kidneys via enzymatic degradation (involving serine proteases, carboxypeptidases, and disulfide oxido-reductases).
- **Elimination**:
  - Inactive metabolites are eliminated in the urine.
- **Half-life & duration of action**:

- Half-life is ~10-30 minutes.

mechanism of vasopressin

- V1 receptor stimulation:
  - Vasoconstriction (including increased responsiveness to alpha-1 agonists).
  - Platelet aggregation.
  - Aldosterone and cortisol release.
- V2 receptor stimulation:
  - Free water reabsorption by the kidney.
  - Release of von Willebrand factor and factor VIII.

physiological effects of vasopressin

- It increases systemic vascular resistance (SVR).
- It does cause *venoconstriction*, which may increase preload.
- Its dominant effect on cardiac output often causes a reduction (but this may depend on the heart's ability to tolerate increased afterload).
- Renal physiology: Vasopressin may preferentially cause vasoconstriction of post-glomerular arterioles in the kidney, causing an increased glomerular filtration rate and a transient increase in renal function. However, it is conceivable that this might force the kidneys to work harder (with an impairment in renal oxygenation). (19572935 (https://pubmed.ncbi.nlm.nih.gov/19572935/))
- Efficacy in acidemia? Traditionally, vasopressin was believed to be more effective than catecholamine vasopressors in acidemia. However, more recent research has challenged this. (35156051 (https://pubmed.ncbi.nlm.nih.gov/35156051/)) Currently, there is no robust, actionable evidence that vasopressin should be especially desirable in acidemia.

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phenylephrine

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- Bradycardia.
- Pulmonary hypertension and/or RV failure. As a pure alpha-agonist, phenylephrine might be the single agent that causes the greatest increase in PVR (e.g., as compared to norepinephrine). (32281470 (https://pubmed.ncbi.nlm.nih.gov/32281470/)) This makes phenylephrine a poor choice for patients with right ventricular failure.
- Profound hypotension (Phenyelphrine is less likely to be effective than more powerful vasopressors such as norepinephrine).

drug-drug interactions

- MAO inhibitors (may increase levels of phenylephrine by up to threefold).

side effects

- **Decreases cardiac output in *selected patients*:**
  - Phenylephrine causes increased preload (venoconstriction) and increased afterload (SVR). Additionally, phenylephrine may cause a *reflex bradycardia* by stimulating the baroreceptor reflex.
  - Reduced cardiac output may occur via two mechanisms:
    - [i] If patients are not preload-responsive, phenylephrine increases the afterload *without* effectively increasing the preload. This may be especially problematic in patients with systolic heart failure who have difficulty tolerating elevated afterload. Alternatively, for a patient who is preload-responsive with a stronger ejection fraction, phenylephrine could cause a net *increase* in cardiac output.
    - [ii] Reduced heart rate may directly decrease cardiac output. This may be the primary mechanism by which phenylephrine decreases cardiac output.
  - 💡 Heart rate may be used to predict the effect on cardiac output. If phenylephrine causes a reflex bradycardia, this often correlates with a reduction in cardiac output. Alternatively, phenylephrine may increase cardiac output if there is no effect on heart rate. (32820475 (https://pubmed.ncbi.nlm.nih.gov/32820475/)) Heart rate reduction indicates that phenylephrine has stimulated a baroreceptor reflex, leading to the

withdrawal of the endogenous sympathetic response to hypotension. (32281470 (https://pubmed.ncbi.nlm.nih.gov/32281470/))

- **Low potency & volume of infusion**. Phenylephrine is about ten times less potent than norepinephrine. Phenylephrine is generally supplied as a relatively *dilute* solution, which can make this logistically problematic for patients requiring high-dose vasoconstriction. Thus, phenylephrine monotherapy is restricted mainly to patients with mild to moderate vasodilatory shock due to logistic constraints.

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indications, advantages 👍

clinical use of phenylephrine

- Vasodilatory shock with an adequate cardiac output.
- Atrial fibrillation with fast ventricular response (increases blood pressure while causing reflex reduction in heart rate). However, one retrospective study of patients with AF who received either norepinephrine or epinephrine found that the difference in heart rates may be *relatively small*. (35526604 (https://pubmed.ncbi.nlm.nih.gov/35526604/))

strengths of phenylephrine

- Reduced risk of arrhythmia, as compared to beta-adrenergic catecholamines.
- Safe for infusion even with tenuous peripheral IV access (relatively low risk of skin necrosis with extravasation).

---

dosing

- Phenylephrine is titrated against MAP.
- Phenylephrine is roughly 10 times less potent than norepinephrine (so 10 mcg/min of phenylephrine is equivalent to 1 mcg/min of norepinephrine).
- The dose range of phenylephrine is typically ~40-180 mcg/min. Consider a more potent vasoconstrictor, such as norepinephrine, for patients who do not respond to high doses of phenylephrine.

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pharmacology

- **Absorption**:
  - IV administration.
- **Distribution**:
  - Vd is ~340 L (more extensive distribution than most pressors).
  - Minimal penetration of the blood-brain barrier due to high hydrophilicity (no stimulatory effects on the brain).
- **Metabolism**:
  - Primarily metabolized into inactive metabolites by monoamine oxidase (MAO-A and MAO-B) and sulfotransferase enzymes (SULT1A3).
- **Elimination**:
  - Inactive metabolites are excreted in the urine.
- **Half-life & duration of action**:
  - With IV infusion, the half-life may be short (~5 minutes) due to rapid tissue uptake.
  - The terminal elimination half-life is ~2-3 hours.
  - In practice, this implies the existence of a context-sensitive half-life. With ongoing phenylephrine administration, accumulation in the tissues may lead to a prolonged and unpredictable half-life. In practice, the half-life may extend out (e.g., to ~20 minutes). (32820475 (https://pubmed.ncbi.nlm.nih.gov/32820475/))

mechanism of action of phenylephrine

- Phenylephrine is a pure alpha-1 agonist.
- Phenylephrine causes *arterial* and *venous* vasoconstriction. This increases both the afterload and the preload.
- Coronary vasoconstriction or vasospasm may result from stimulation of alpha-1D receptors.
- Heart rate: Phenylephrine can cause mild reflex bradycardia due to an elevation in blood pressure.

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norepinephrine

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contraindications, drug interactions, side effects 👎

contraindications

- There are few contraindications to norepinephrine. This makes norepinephrine a good choice for *undifferentiated shock*.
- Mesenteric or peripheral vascular thrombosis (relative contraindication).
- Sulfite sensitivity (some preparations).

drug-drug interactions

- MAO inhibitors, including isocarboxazid, phenelzine, tranylcypromine, linezolid, and methylene blue (effects may be exaggerated and prolonged; titrate accordingly). (Peck 2021)
- COMT inhibitors may reduce norepinephrine metabolism.

side effects

- Increased myocardial oxygen consumption (promoting myocardial ischemia).
- Mesenteric vasoconstriction.
- Excessive vasoconstriction in the context of heart failure may decrease perfusion (especially when combined with vasopressin).
- Bradycardia (may reflect a reflex result of a rise in BP). (Wellington 3e)
- Hyperglycemia (reduced insulin sensitivity).
- Extravasation (peripheral administration).

---

indications, advantages 👍

clinical use of norepinephrine

- Vasodilatory shock states are the most logical application, e.g.:
    - Septic shock.

    - Systemic inflammatory states (e.g., pancreatitis).
    - Neurogenic shock.
- Cardiogenic shock with hypotension:
    - Norepinephrine may be utilized to establish an adequate MAP.
    - Other interventions are often required to support perfusion (e.g., mechanical support or inotropes).
    - OptimaCC was a pilot RCT comparing norepinephrine vs. epinephrine for the treatment of post-MI cardiogenic shock. Patients treated with epinephrine had a greater rate of "refractory shock," but this definition included lactate elevation (a known side-effect of epinephrine infusions). (29976291 (https://pubmed.ncbi.nlm.nih.gov/29976291/)) Patients treated with epinephrine had a greater cardiac index, driven primarily by a higher heart rate (rather than a higher stroke volume). There was a trend towards reduced mortality among patients treated with norepinephrine.
- Norepinephrine is often used as a "broad-spectrum" vasoactive agent for undifferentiated hypotensive patients.

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dosing

- Norepinephrine is titrated against blood pressure (usually MAP).
- The usual dose range is up to 30 ug/min.
- There is no "maximal dose" of norepinephrine. (https://emcrit.org/pulmcrit/high-dose-vasopressor/)

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pharmacology

- **Absorption**:
    - IV administration.
    - Steady-state plasma concentrations are reached in ~5 minutes.
- **Distribution**:
    - Protein binding is only 25%.

    - Vd is 9 liters.
    - Doesn't cross the blood-brain barrier.
- **Metabolism**:
    - Extensively metabolized in the liver, lungs, and other tissues by COMT (catechol-O-methyltransferase) and MAO (monoamine oxidase).
    - Norepinephrine is also taken up by presynaptic nerve terminals via the norepinephrine transporter (NET).
- **Elimination**:
    - Inactive metabolites are excreted in the urine.
- **Half-life & duration of action**:
    - Half-life of ~2.5 minutes.

mechanism of action of norepinephrine

- Norepinephrine functions *predominantly* as an alpha-agonist, resulting in:
    - Increased SVR (afterload).
    - Venoconstriction that increases preload.
- Norepinephrine also has some beta-1 agonism (which exerts mild inotropic and chronotropic effects).
- Norepinephrine stimulates alpha-2 receptors, reducing further norepinephrine release from presynaptic neurons as a negative feedback mechanism. (Hernandez 2024)

physiologic effects include

- Norepinephrine increases blood pressure.
- In sepsis, norepinephrine usually increases renal blood flow and urine output. (Irwin & Rippe 9e)
- Effects on cardiac output are similar to those of phenylephrine, although some beta-adrenergic activity may allow norepinephrine to have a somewhat more favorable impact on cardiac output.
    - Norepinephrine increases preload (venous return) and afterload. If the heart is preload/fluid sensitive, the norepinephrine may have a neutral or positive effect on cardiac output. However, in the context of a failing heart that isn't preload-dependent, *norepinephrine may decrease cardiac output by increasing afterload*. (32281470 (https://pubmed.ncbi.nlm.nih.gov/32281470/))

- Norepinephrine exerts some beta-1 activity, which may increase heart rate. However, this is often counterbalanced by reflex bradycardia resulting from increased blood pressure. (Irwin & Rippe 9e)

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epinephrine

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- Tachycardia.
- Arrhythmias.
- Profound acidosis (epinephrine increases lactate production, may worsen pH).
- Clinicians are using lactate to track disease severity (epinephrine increases lactate levels, rendering this essentially impossible).
- LV outflow tract obstruction (LVOTO).

drug-drug interactions

- COMT inhibitors (may increase levels of epinephrine).
- MAO inhibitors (may increase levels of epinephrine).

side effects

- Myocardial ischemia, arrhythmias, and/or stress cardiomyopathy (due to combined beta-1 and beta-2 stimulation). However, interestingly, one study found that epinephrine at 2 mcg/min caused less tachycardia than dobutamine dosed at 5 mcg/kg/min. (1421064 (https://pubmed.ncbi.nlm.nih.gov/1421064/))
- Hypertension.
- Complications of beta-2 stimulation:
  - Hyperglycemia.

- Hypokalemia (beta-2 adrenergic activity causes potassium to shift into cells).
- Epinephrine stimulates lactate production. This is generally not *dangerous* (but may indeed be physiologically beneficial). 🌊 (https://emcrit.org/pulmcrit/understanding-lactate-in-sepsis-using-it-to-our-advantage/) However, some aspects of this are notable:
  - [i] Using epinephrine makes it impossible to use lactate as an indication of occult shock. If trending lactates is important in your practice (e.g., in managing cardiogenic shock patients), then an epinephrine infusion may confound this.
  - [ii] For patients with severe and uncontrolled acidosis, lactic acidosis may be problematic (e.g., severe metformin-induced lactic acidosis).
- Diaphoresis.
- Tremor.
- Patients feel bad: Epinephrine can cause anxiety, palpitations, tremors, pallor, diaphoresis, nausea/vomiting, and an overall sense of feeling unwell.

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indications, advantages 👍

clinical uses of epinephrine

- **Bradycardia** and bradycardic shock. Epinephrine is particularly useful in patients with bradycardia plus hyperkalemia (e.g., BRASH syndrome 📖 (https://emcrit.org/ibcc/brash/#top)).
- **Septic shock**:
  - RCTs have demonstrated that epinephrine is a reasonable alternative to either norepinephrine or the combination of norepinephrine plus dobutamine. (18654759 (https://pubmed.ncbi.nlm.nih.gov/18654759/) , 17720019 (https://pubmed.ncbi.nlm.nih.gov/17720019/)) However, sepsis encompasses a range of hemodynamic endotypes – only *some* of which may be optimally treated with epinephrine.
  - Epinephrine may be a rational choice for patients with inappropriately low heart rate and/or low cardiac output (e.g., elderly patients who fail to mount an endogenous sympathetic response to sepsis). 🌊 (https://emcrit.org/pulmcrit/epinephrine-challenge-septic-shock/)

    - For patients with purely vasodilatory shock with a hyperkinetic heart, epinephrine *isn't* a good choice (since it functions predominantly as an *inotrope* at lower doses).
- **Status post cardiopulmonary bypass**: Low-dose epinephrine may be utilized as an inotrope that will not decrease the SVR.
- **Inotrope**: Epinephrine is often used as a front-line inotrope for post-cardiotomy patients with low cardiac output. (Bojar 2021)
- **Push-dose epinephrine** is useful for patients crashing from a variety of causes (e.g., bradycardic peri-arrest). Epinephrine is generally a good choice for the nearly-dead patient. 🌊 (https://emcrit.org/pulmcrit/epinephrine-atropine-bradycardia/)
- **Anaphylaxis**: Epinephrine is the front-line treatment of choice. Note that epinephrine is indicated for the treatment of anaphylaxis *even if the hemodynamics are stable*. 📖 (https://emcrit.org/ibcc/anaphylaxis/)
- **Asthma**: Beta-2 adrenergic effects may be used for patients with severe asthma who may have so much bronchoconstriction that inhaled medications are ineffective.
- **Inhaled [racemic] epinephrine**: For management of airway edema.

combination of epinephrine with other agents

- 👍 Epinephrine + vasopressin is often helpful in septic shock or right ventricular failure.
    - Epinephrine provides chronotropism and inotropism.
    - Vasopressin increases the systemic vascular resistance (SVR) without increasing the pulmonary vascular resistance (PVR).
- 👍 Epinephrine + milrinone may be considered for patients needing additional inotropy and not responding to low-dose epinephrine. Low-dose milrinone plus epinephrine can yield synergistic inotropic effects with a relatively neutral impact on MAP. (32281470 (https://pubmed.ncbi.nlm.nih.gov/32281470/))
- 👎 Epinephrine + dobutamine may not be a great combination. Limited clinical evidence suggests that dobutamine doesn't add significant efficacy on top of epinephrine. (9667293 (https://pubmed.ncbi.nlm.nih.gov/9667293/)) Using two drugs that compete for beta-2 receptors is probably not helpful; choosing one catecholamine inotrope (either epinephrine or dobutamine) is better.

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dosing schema for epinephrine

- **Low/inotropic dose epinephrine** (perhaps <4-8 ug/minute or <0.05-0.08 ug/kg/min): (Gutierrez 2024; Irwin & Rippe 9e)
  - The *predominant* effect is as an inotrope, so it can be used for patients with low-output cardiogenic shock (with dose escalation, epinephrine has a more significant impact on alpha-receptors).
  - At low doses, epinephrine may have little effect on SVR (beta-agonist effects will decrease SVR, whereas mild alpha-agonist effects will increase SVR). The net result might be a pure inotrope that doesn't cause systemic vasodilation. Thus, epinephrine monotherapy may be an alternative to the combination of norepinephrine plus dobutamine for patients with hypotension and cardiogenic shock.
  - Low-dose epinephrine may also be sufficient as maintenance therapy for anaphylaxis or status asthmaticus.
- **Higher doses**:
  - With up-titration, epinephrine has greater alpha-agonist effects.

STAT home-made epinephrine infusion

- If a pre-mixed bag of epinephrine isn't immediately available, one may be created as follows:
- Inject a 10-ml syringe of cardiac epinephrine (1:10,000) into a 1-liter bag of normal saline or lactated Ringer's. (Or a 1-ml vial of 1:1,000 epinephrine – *either* form will work perfectly here, since both contain a total of 1 mg of epinephrine). Shake it up. This creates a **1 microgram/ml solution** of epinephrine.
- Titrate infusion:
  - **2 micrograms/min** = **120 ml/hour**.
  - 5 micrograms/min = 300 ml/hour.
  - **10 micrograms/min** = **600 ml/hour**.
  - **16 micrograms/min** = **960 ml/hour**.
- Push doses of epinephrine:

    - **20 mcg** = **20 ml bolus** (using a 20 cc syringe).
- 💡 Diluting epinephrine in a liter of saline makes it difficult to give it fast enough to kill someone. Even if this solution is run in wide open, it will result in administration of ~20-30 mcg/min infusion (which shouldn't be dangerous in a monitored setting and might be an appropriate dose during the first few minutes).

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pharmacology

- **Absorption**:
    - IV: 100% bioavailability, onset in <5 minutes.
    - IM: 5-10 minute onset (mid-anterolateral thigh works faster than deltoid).
    - SC: 20-30 minutes onset (not recommended).
- **Distribution**:
    - Vd ~8 liters (circulating plasma volume).
    - Protein binding is ~50%.
- **Metabolism**:
    - Metabolized through two pathways:
        - Dominant route: COMT (catechol-O-methyltransferase) converts epinephrine into metanephrine and normetanephrine.
        - Secondary route: MAO (monoamine oxidase) converts epinephrine into vanillylmandelic acid (VMA).
    - Both COMT and MAO are widely distributed in the liver, kidneys, and other extraneuronal tissues. Relative contributions may be roughly: liver (~30%), kidneys (~25%), skeletal muscle (20%), mesenteric organs (10%).
    - The pharmacokinetics of epinephrine remain *linear* (even at high doses).
- **Elimination**:
    - Urinary excretion predominantly as metabolites (vanillylmandelic acid, metanephrines).
- **Half-life & duration of action**:
    - Half-life of ~2-4 minutes.

physiology of epinephrine

- [1] Beta-1 and Beta-2 activity in the myocardium causes:
  - Positive chronotropy.
  - Positive inotropy.
- [2] Alpha activity causes:
  - Increased SVR.
  - Venoconstriction (increasing preload).
- [3] Beta-2 activity (*unlike* norepinephrine or dobutamine) causes:
  - [i] Bronchodilation.
  - [ii] Potassium shifts into cells. Effects on potassium may be helpful in patients with hyperkalemia and bradycardia (e.g., BRASH syndrome 📖 (https://emcrit.org/ibcc/brash/#top)).
  - [iii] Glycogenolysis and potentially hyperglycemia.
  - [iv] Aerobic lactate production in the liver.
  - [v] This is often feared, but lactate may be used as a metabolic fuel by the heart. Hence, this mechanism of action is probably beneficial (in the absence of profound pre-existing metabolic acidosis). 🌊 (https://emcrit.org/pulmcrit/understanding-lactate-in-sepsis-using-it-to-our-advantage/)
  - [vi] Myocardial stimulation (the myocardium contains beta-1 and beta-2 receptors; this could theoretically make epinephrine a stronger inotrope, especially in patients previously treated with chronic beta-1 agonists such as dobutamine).
  - [v] Reduction in pulmonary vascular resistance (PVR). (30582447 (https://pubmed.ncbi.nlm.nih.gov/30582447/))
- [4] Mast cell stabilization (this is useful in anaphylaxis).

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methylene blue (MB)

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- [1] Hemodynamics (*if* methylene blue is being use to treat shock):
  - Severe pulmonary hypertension (methylene blue will increase pulmonary vascular resistance).
  - Cardiogenic shock (increased afterload may promote pulmonary edema).
  - Hypovolemic shock (excessive afterload could reduce cardiac output).
- [2] Risk of serotonin syndrome (e.g., recent use of selective serotonin reuptake inhibitors, high-dose fentanyl). (28655448 (https://pubmed.ncbi.nlm.nih.gov/28655448/))
  - Methylene blue inhibits monoamine oxidase A (MAO), increasing brain serotonin levels.
  - Medications that can cause serotonin syndrome are listed here: 📖 (https://emcrit.org/ibcc/serotonin/#causes_of_serotonin_syndrome)
- [3] G6PD deficiency (glucose-6-phosphate dehydrogenase deficiency) – personal or family history.
  - Methylene blue can act as an oxidizing agent at high doses (e.g., >7 mg/kg). This may cause methemoglobinemia. In patients with G6PD deficiency, this could also lead to hemolytic anemia.
- [4] Poor IV access (relative contraindication): Methylene blue can cause tissue necrosis if it extravasates. Ideally, methylene blue should be infused via a central line. Dilution in larger volumes of carrier solution might also reduce this risk (e.g., 100 mg diluted in 500 ml saline).
- [5] Pregnancy (FDA class X): Reports describe neonatal intestinal atresia and fetal death after *intra-amniotic injection* of methylene blue during the second trimester. When administered close to delivery, fetal risks may include hemolytic anemia and methemoglobinemia. For life-threatening acquired methemoglobinemia during pregnancy, the benefits may outweigh the risks.
  - (Further discussion on administration of methylene blue in pregnancy is here (https://emcrit.org/ibcc/methemoglobinemia/#treatment_in_pregnancy) .)

drug-drug interactions

- Serotonergic agents (methylene blue inhibits MAO-A, which may promote serotonin syndrome).
- Methylene blue inhibits several cytochrome P450 enzymes (CYP1A2, 2B6, 2C8, 2C19, 2D6, and 3A4/5), UGT enzymes (UGT1A4, UGT1A9), is a substrate and inhibitor of P-

glycoprotein, and may inhibit renal transporters (OCT2, MATE1, and MATE2-K). However, 2 mg/kg doses of methylene blue don't seem to affect common CYP enzymes substantially.

side effects

- Vasoconstrictive side-effects consistent with the pressor effect:
  - Mesenteric vasoconstriction may occur. (38365828 (https://pubmed.ncbi.nlm.nih.gov/38365828/))
  - Extravasation may cause skin necrosis.
- Serotonin syndrome (discussed above).
- Hemolytic anemia in G6PD deficiency (discussed above).
- The patient turns blue; this may reflect one or more of the following possibilities:
  - [1] Methemoglobinemia.
    - [a] Underlying methemoglobinemia (which existed prior to therapy with methylene blue).
    - [b] Using very high doses of methylene blue may *cause* methemoglobinemia.
    - [c] Using methylene blue in patients with underlying G6PD deficiency may cause methemoglobinemia.
  - [2] High levels of methylene blue *itself* may cause blue discoloration of skin (may be confused with methemoglobinemia).
  - To sort out methemoglobinemia versus methylene blue dye itself:
    - Check a methemoglobin level.
    - Visual evaluation of the color of the blood (methemoglobin may cause the blood to appear *brown*, whereas methylene blue will cause it to be *blue*).

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indications, advantages 👍

general indications for methylene blue

- [1] Refractory vasoplegic shock of any etiology.
  - *Especially* following cardiothoracic surgery.
  - Possibly also: septic shock, anaphylaxis.
- [2] Metformin poisoning. 📖 (https://emcrit.org/ibcc/metformin/#methylene_blue??)

- [3] Treatment of methemoglobinemia, with the following specific indications:.
  - [1] Symptomatic methemoglobinemia.
  - [2] Methemoglobin level >30%.
  - [3] Possibly: Methemoglobin level >10-20% in patients who are less likely to tolerate reduced oxygen delivery. (32193811 (https://pubmed.ncbi.nlm.nih.gov/32193811/))
- [4] Ifosfamide-induced encephalopathy. (Paw and Shulman 2025)

role of methylene blue in therapy for septic shock

- Methylene blue was historically utilized as a salvage therapy for patients refractory to all other treatments. However, a recent meta-analysis of RCTs found a mortality benefit from methylene blue (when combining patients with septic shock and patients with post-surgical vasoplegia). (37880041 (https://pubmed.ncbi.nlm.nih.gov/37880041/)) A single-center RCT found that early methylene blue administration accelerated shock resolution, subsequently reducing ICU length of stay. (36915146 (https://pubmed.ncbi.nlm.nih.gov/36915146/)) These studies suggest that an earlier introduction of methylene blue into therapy could be reasonable. However, methylene blue has yet to demonstrate efficacy in a large, multicenter, randomized controlled trial.
- Methylene blue appears to be a reasonably safe therapy if appropriate caution is exercised regarding drug-drug interactions, contraindications (listed above), and cumulative dose (ideally maintained below ~5 mg/kg and spread out over time). Extravasation with skin necrosis does remain a concern, even at lower doses. Consequently, it might be reasonable to consider methylene blue for patients who fail to respond well to vasopressors and have central vascular access.

---

dosing

some general comments

- ⚠️ If administered rapidly, methylene blue will temporarily cause spuriously low pulse oximetry results.
- ⚠️ Doses >7 mg/kg may cause numerous side effects (nausea, vomiting, confusion, dyspnea, tremulousness, diaphoresis, methemoglobinemia, hemolytic anemia).
- **Renal dysfunction**: In moderate-to-severe impairment, consider dose adjustment.

MB dose in septic shock

- The usual dose is 1-2 mg/kg (e.g., 100 mg). Depending on patient acuity, this may be infused over a variable time frame (from 5 minutes to six hours). The largest RCT investigating methylene blue in septic shock utilized 100 mg doses diluted in 500 ml saline that was infused over 6 hours every day for three days. (36915146 (https://pubmed.ncbi.nlm.nih.gov/36915146/))
- If administered as a bolus, the effects will often wane after >2-3 hours. (Paw and Shulman 2025)

MB dose in post-cardiotomy vasoplegic shock

- Loading dose: 1-2 mg/kg IV over 15 minutes.
- Infusion: 0.5 mg/kg infusion for six hours. (Bagchi 2025)

MB infusion for refractory shock states

- Studies have described infusions ranging from 0.25 – 1 mg/kg/hour. (29329694 (https://pubmed.ncbi.nlm.nih.gov/29329694/))
- Infusions can be continued for up to 48-72 hours, with weaning off based on hemodynamics.
- Infusion increases the risk of drug accumulation, so this should probably be limited to refractory shock. The half-life of methylene blue may range from ~5 to 24 hours, casting some doubt on whether an ongoing infusion is pharmacokinetically necessary. An alternative strategy is to repeat 1-2 mg/kg q4-6 hours as needed. (29329694 (https://pubmed.ncbi.nlm.nih.gov/29329694/))

MB dose for metformin toxicity

- A reasonable dose might be a 2 mg/kg loading dose over 15-30 minutes, followed by an infusion of ~0.25 mg/kg/hour. (26150642 (https://pubmed.ncbi.nlm.nih.gov/26150642/))
- Patients often have *renal failure*, so be thoughtful about the risk of methylene blue accumulation over time, and wean the infusion as soon as possible.

MB dose for methemoglobinemia

- **Initial dose:**

    - Give 2 mg/kg IV over 5 minutes.
    - Clinical improvement should occur within minutes. However, methylene blue may cause transient drops in the measured oxygen saturation (due to its blue pigment). Cyanosis should resolve within an hour.
- **Re-dosing:**
    - Repeat dosing may be needed after 60 minutes if the initial dose is ineffective (e.g., persistent cyanosis). However, failure to respond to a dose of 2 mg/kg raises questions of G6PD deficiency. This can get tricky because methylene blue can interfere with the assay for methemoglobin (so *avoid* checking a methemoglobin level immediately after giving methylene blue).
    - Rebound methemoglobinemia can occur in 4-12 hours. Rebound may reflect the persistence of the causative agent (e.g., large volume ingestion). This may be treated with another dose of methylene blue (e.g., 1 mg/kg).
    - For repeated rebounding methemoglobinemia, a continuous infusion of methylene blue may be required at a dose of 0.1-0.25 mg/kg/hr (0.1 mg/kg/hr is usually sufficient; this may be required for days with intermittent efforts to wean off). (34467556 (https://pubmed.ncbi.nlm.nih.gov/34467556/)) (https://emcrit.org/toxhound/refractory-methemoglobinemia/)

---

pharmacology

- **Absorption**:
    - IV administration.
- **Distribution**:
    - Vd is large (250 L), including distribution to the brain.
    - Protein binding is ~95%.
    - Concentration-dependent partitioning into erythrocytes (initially, after a dose, methylene blue is taken up by erythrocytes).
    - Methylene blue is a P-glycoprotein substrate.
- **Metabolism**:
    - ~60% of methylene blue is metabolized in the liver.

    - Metabolism is primarily via UGT-mediated conjugation (especially UGT1A4 and UGT1A9).
    - Minor metabolism via CYP 1A2, 2C19, and 2D6.
- **Elimination**:
    - ~40% is excreted unchanged in the urine.
    - Renal dysfunction increases methylene blue exposure; however, the half-life remains similar in mild-to-moderate renal dysfunction.
- **Half-life & duration of action**:
    - Half-life may range from ~5-24 hours (with varying data in different sources). (38365828 (https://pubmed.ncbi.nlm.nih.gov/38365828/))

mechanisms of action

- [1] Methylene blue causes vasoconstriction by inhibiting nitric oxide synthase:
    - This is a potentially hazardous method for increasing blood pressure, as it may compromise microvascular perfusion.
    - Historically, a nitric oxide synthesis inhibitor was shown to increase mortality in septic shock. (14707556 (https://www.ncbi.nlm.nih.gov/pubmed/14707556))
- [2] Methylene blue inhibits guanylate cyclase, thereby blocking the conversion of guanosine triphosphate to cGMP (an intracellular signaling molecule that increases vasodilation).
- [3] Methylene blue may accept electrons from NADH and transfer them to cytochrome C in the mitochondria, *bypassing* parts of the electron transport chain. This could restore mitochondrial function in certain situations where parts of the electron transport chain are dysfunctional, such as metformin toxicity. (28840449 (https://pubmed.ncbi.nlm.nih.gov/28840449/))

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hydroxocobalamin

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- Continuous renal replacement therapy:
  - Hydroxocobalamin can cause some hemodialysis machines to malfunction.
- Pulmonary HTN? (Based on its mechanism, it would be predicted to increase PVR.)
- Laboratory artifacts may occur: (37225547 (https://pubmed.ncbi.nlm.nih.gov/37225547/), 38030578 (https://pubmed.ncbi.nlm.nih.gov/38030578/))
  - Elevation of:
    - Alkaline phosphatase.
    - Bilirubin.
    - Creatinine.
    - Glucose.
    - Hemoglobin (but not hematocrit).
  - Unpredictable effect on:
    - Lactate dehydrogenase.
    - aPTT and PT/INR. (Bagchi 2025)
- Acute kidney injury (relative).

drug-drug interactions

- No pharmacokinetic drug-drug interactions.
- Hydroxocobalamin can interfere with some tests used to monitor other medications.

side effects

- Renal complications:
  - Acute kidney injury. (38030578 (https://pubmed.ncbi.nlm.nih.gov/38030578/))
  - Calcium oxalate stone formation. (38030578 (https://pubmed.ncbi.nlm.nih.gov/38030578/))
- Nausea.
- Lymphocytopenia. (38202178 (https://pubmed.ncbi.nlm.nih.gov/38202178/))
- Angioedema, anaphylaxis. (Bagchi 2025)
- Flushing or redness of the skin (especially face and upper chest).

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indications, advantages 👍

- [1] Refractory vasodilatory shock, potentially including:
  - Postoperative vasoplegia.
  - Drug-induced vasoplegia.
  - Refractory septic shock (supported by a pilot trial showing reduced vasopressor requirements and animal studies showing improved survival). (36174744 (https://pubmed.ncbi.nlm.nih.gov/36174744/))
- [2] Cyanide toxicity.
- Hydroxocobalamin may be preferred over methylene blue in patients with contraindications to methylene blue, including: (37225547 (https://pubmed.ncbi.nlm.nih.gov/37225547/))
  - G6PD deficiency.
  - Risk for serotonin syndrome.
  - (Additional contraindications to methylene blue are listed in the section above.)

---

dosing

- The usual dose is 5 grams IV over 10-15 minutes (this is the dose in Cyanokit). (37225547 (https://pubmed.ncbi.nlm.nih.gov/37225547/)) However, some reports describe the use of 10 grams. (38202178 (https://pubmed.ncbi.nlm.nih.gov/38202178/))
- Most studies describe the use of a *single dose* of hydroxocobalamin. (38030578 (https://pubmed.ncbi.nlm.nih.gov/38030578/))
- Post-cardiotomy vasoplegic syndrome: Start with 5 grams IV over 15 minutes. If no response is seen, a second dose may be administered. (Bagchi 2025)

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pharmacology

- **Absorption**:
  - IV administration.
- **Distribution**:

    - Vd is ~300 L for free cobalamin-III, and 25 L (0.45 L/kg) for total cobalamin-III.
    - Extensive binding to plasma proteins.
    - Hydroxocobalamin is very rapidly taken up by cells (faster than cyanocobalamin), which is an advantage in the treatment of cobalamin deficiency states.
- **Metabolism**:
    - Hydroxocobalamin doesn't undergo metabolism.
    - In cyanide poisoning, hydroxocobalamin binds to cyanide to form cyanocobalamin (which is also not metabolized).
- **Elimination**:
    - ~65% of the administered dose is excreted unchanged in the urine.
    - Biliary elimination and enterohepatic recycling also occur.
- **Half-life & duration of action**:
    - Half-life may be ~26-31 hours. (37225547 (https://pubmed.ncbi.nlm.nih.gov/37225547/))

pharmacodynamics

- Hydroxocobalamin is a synthetic B12 vitamin analog that is administered intravenously.
- Hydroxocobalamin inhibits nitric oxide directly and also inhibits nitric oxide synthase. It might also function by eliminating the endogenous vasodilator hydrogen sulfide (H2S). (37225547 (https://pubmed.ncbi.nlm.nih.gov/37225547/))

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angiotensin II

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- Non-vasodilatory shock states (e.g., cardiogenic shock).
- High risk for DVT/PE.

drug-drug interactions

- ACE inhibitors: patients may become increasingly *sensitive* to the effects of angiotensin II (note that ACE inhibitors *don't* affect ACE2, and therefore *don't* alter the metabolism of angiotensin II).
- ARB (angiotensin receptor blockers): may *attenuate* the effect of angiotensin-II (by blocking the angiotensin-1 receptor).
- There are no pharmacokinetic drug-drug interactions.

side effects

- Peripheral ischemia.
- Thrombotic events (both arterial and venous):
  - DVT/PE.
  - MI.
- Reduced cardiac output in selected patients: The physiology here is largely *the same as with phenylephrine or vasopressin*. The effect of pure vasoconstrictors on cardiac output is discussed in the section on *phenylephrine drawbacks*. ⚡ (#phenylephrine)
- Bronchoconstriction may occur in susceptible patients.

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indications, advantages 👍

- Angiotensin II may be used for refractory vasodilatory shock, especially:
  - Post-cardiotomy vasoplegic syndrome (*after* the patient is on ≧15 mcg/min NE, ≧0.04 U/min vasopressin, methylene blue, and hydroxocobalamin).
  - ACE-inhibitor overdose.
- The use of vasopressin appears to improve responsiveness to angiotensin II. In practice, angiotensin II should only be utilized among patients *already* on vasopressin.

---

dosing

- Stabilization:
  - Start at 20 ng/kg/min.

    - May up-titrate by 10-15 ng/kg/min every 5 minutes to a maximal initial dose of 80 ng/kg/min. This dose may be maintained for up to three hours.
- Maintenance:
    - Only continue angiotensin II if the patient responds favorably to it.
    - Following stabilization, the maintenance dose shouldn't exceed 40 ng/kg/min.
    - Doses as low as 1.25 ng/kg/min can be utilized.

---

pharmacology

- **Absorption**:
    - IV administration.
    - BP target may be achieved ~5 minutes after initiation.
- **Distribution**:
    - Tissue levels may *exceed* plasma concentrations due to receptor-mediated uptake.
- **Metabolism**:
    - Angiotensin II is a small octapeptide hormone.
    - Angiotensin II is degraded via various pathways:
        - Aminopeptidase A metabolism yields angiotensin III. Angiotensin III retains ~40% of the parent molecule's activity at AT1 receptors.
        - Angiotensin-converting enzyme 2 (ACE2) metabolism yields angiotensin-(1-7). This *counteracts* angiotensin II via vasodilation.
- **Elimination**:
    - Excretion pathways of Angiotensin III and angiotensin-(1-7) are poorly characterized.
    - Clearance isn't significantly affected by renal or hepatic dysfunction, since elimination is primarily due to proteolytic breakdown rather than organ excretion.
- **Half-life & duration of action**:
    - The serum half-life is under a minute. However, the half-life of tissue activity may extend to 15-30 minutes due to localized enzymatic activity.

mechanism

- [1] Angiotensin II binds to angiotensin II-receptor type-1 on the vascular smooth muscle cells, stimulating Ca/calmodulin-dependent phosphorylation of myosin. This leads to

smooth muscle contraction and vasoconstriction.
- [2] Angiotensin II stimulates the production of aldosterone.

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midodrine

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- Bradycardia.
- Low-output shock states.
- Renal failure (relative) – may accumulate, especially in patients requiring hemodialysis.
- Urinary retention (alpha-adrenergic agonist activity may exacerbate).

drug-drug interactions

- Drugs eliminated by active renal tubular secretion (e.g., procainamide, flecainide, quinidine) may compete for renal excretion.

side effects

- Reflex bradycardia may be the most notable side effect.
- Ischemic bowel complications have been reported. (39726934 (https://pubmed.ncbi.nlm.nih.gov/39726934/))
- Urinary retention.
- Midodrine is an alpha-1 agonist, so it has contraindications and problems similar to phenylephrine. ⚡ (#phenylephrine)

---

indications, advantages 👍

- **Cirrhosis & hepatorenal syndrome**:
  - Midodrine is a component of oral therapy for hepatorenal syndrome.
  - Some evidence suggests that *ongoing* midodrine therapy in patients with cirrhosis may support renal perfusion (given that these patients suffer from chronic vasodilation).
- **Orthostatic hypotension and dysautonomia**.
- **Intradialytic hypotension**.
- **Accelerated weaning from vasopressors**:
  - ⚠️ The MIDAS trial suggests that midodrine is *not* effective at accelerating the weaning off IV vasopressors among most ICU patients. 🌊 (https://www.thebottomline.org.uk/summaries/midas/) (32885276 (https://pubmed.ncbi.nlm.nih.gov/32885276/))
  - ⚠️ Currently, the best available evidence indicates that midodrine should *not* be used for most patients to hasten weaning off vasopressor infusions.

---

dosing

- The usual starting dose is 10 mg PO q8hr. *Make sure the drug is dosed q8hr and not "three times daily with meals," which is what the computer may default to.*
- The usual dose range is 5-40 mg q8hr. (26953217 (https://pubmed.ncbi.nlm.nih.gov/26953217/)) However, the dose should be titrated to effect, with adequate doses sometimes exceeding 120 mg per day. (39110210 (https://pubmed.ncbi.nlm.nih.gov/39110210/))
- Given a short half-life of only 3-4 hours, shorter dosing intervals (q6hr) could be rational to avoid breakthrough hypotension (e.g., 30 mg q6hr rather than 40 mg q8hr). (39726934 (https://pubmed.ncbi.nlm.nih.gov/39726934/))

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pharmacology

- **Absorption**:
  - Oral bioavailability is 93% (facilitated by intestinal H+-coupled peptide transporter 1, PEPT1).

    - The peak plasma concentration of midodrine occurs after ~30 minutes.
- **Distribution**:
    - Protein binding is not significant.
    - Desglymidodrine doesn't penetrate the blood-brain barrier.
- **Metabolism**:
    - Midodrine is a prodrug that is rapidly metabolized via enzymatic hydrolysis (deglycination), yielding its active metabolite, desglymidodrine. Hydrolysis occurs in systemic circulation and multiple tissues and is efficient.
    - Levels of desglymidodrine peak after 1-2 hours, with a half-life of 3-4 hours. (39726934 (https://pubmed.ncbi.nlm.nih.gov/39726934/))
    - Desglymidodrine is ~80% excreted unchanged in the urine. However, ~20% may undergo 5'-O-demyethylation via CYP2D6, CYP1A2, and CYP2C1.
- **Elimination**:
    - Desglymidodrine is primarily (~80%) eliminated by the kidneys, mostly via active renal secretion.
- **Half-life & duration of action**:
    - Midodrine has a half-life of ~30 minutes, but it is a prodrug, so this is less clinically relevant.
    - Desglymidodrine has a half-life of 3-4 hours (which is prolonged in renal dysfunction).

mechanism

- Oral alpha-1 agonist, which acts as a pure vasopressor.

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droxidopa

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- Contraindications and cautions are generally similar to those of norepinephrine. Potential contraindications could include unstable atrial or ventricular tachyarrhythmias.

drug-drug interactions

- Dopa decarboxylase inhibitors (e.g., carbidopa) will impair the conversion of droxidopa into norepinephrine, thereby reducing its efficacy.
- MAO inhibitors (e.g., isocarboxazid, tranylcypromine) could theoretically increase norepinephrine levels, thereby further elevating blood pressure.
- Norepinephrine transport inhibitors (e.g., duloxetine, venlafaxine, atomoxetine, bupropion) could theoretically increase BP.

side effects

- A syndrome complex resembling neuroleptic malignant syndrome (including hyperpyrexia and confusion).
- Ischemic bowel complications.
- Nausea.

---

indications, advantages 👍

- Droxidopa is emerging as the preferred oral agent to facilitate weaning off IV vasopressors. Compared to midodrine, droxidopa has the following advantages:
    - [1] Droxidopa provides both alpha- and beta-adrenergic stimulation (thereby avoiding issues with reflex bradycardia).
    - [2] Droxidopa's effect on blood pressure may last longer than midodrine's, thereby reducing the likelihood of breakthrough hypotension.
- Droxidopa is also indicated for *neurogenic orthostatic hypotension* (seen in Parkinson's disease, Lewy body dementia, high spinal cord injury, diabetes, amyloidosis, or multiple system atrophy).

---

dosing

- **Neurogenic orthostatic hypotension**:
  - Start with 100 mg PO TID
  - Titrate in increments of 100 mg daily.
  - Max dose 600 mg PO TID.
- **Vasopressor weaning for persistent vasoplegic shock**:
  - ⚠️ This indication has not yet been studied in a prospective RCT.
  - This generally starts at 100 mg PO TID and escalates as high as 800 mg TID (2400 mg/d). The required dose to achieve vasopressor liberation is typically 200-400 mg three times daily. (37838507 (https://pubmed.ncbi.nlm.nih.gov/37838507/) , 37838507 (https://pubmed.ncbi.nlm.nih.gov/37838507/))
  - The pressor effect lasts for ~6 hours, so it might be more rational to dose this q6hr (e.g., ~100-400 mg q6hr). (26092297 (https://pubmed.ncbi.nlm.nih.gov/26092297/))
  - The time to vasopressor discontinuation is often several days after initiation, possibly related to the need for dose escalation over time. Consequently, if the patient is making no progress with vasopressor weaning, it may be rational to start the dose-escalation process sooner rather than later.

---

pharmacology

- **Absorption**:
  - Oral bioavailability is 90%.
  - Capsules may be opened and administered via a feeding tube. (39726934 (https://pubmed.ncbi.nlm.nih.gov/39726934/))
  - Peak plasma concentration of droxidopa occurs within 1-4 hours.
- **Distribution**:
  - Protein binding is 75% at 100 ng/mL and 26% at 10,000 ng/mL.
  - Vd is ~200 L.
  - Droxidopa seems to be able to cross the blood-brain barrier.
- **Metabolism**:
  - Various metabolic pathways:
    - Methylation by COMT (catechol-O-methyltransferase) yields 3-O-methyldihydroxyphenylserine (3-OM-DOPS). This may be the major metabolite.

        - Dopa-decarboxylase (aka L-aromatic amino acid decarboxylase) yields norepinephrine.
        - DOPS aldolase cleaves it to yield protocatechualdehyde.
    - The pharmacologic effect is mediated by norepinephrine (not the parent drug droxidopa).
    - Metabolism occurs in peripheral tissues.
- **Elimination**:
    - The primary route of elimination is renal.
    - ~75% of a dose is excreted in the kidneys, mainly as 3-OM-DOPS.
- **Half-life & duration of action**:
    - Half-life is ~2.5 hours.
    - The pressor effect appears after one hour, peaks at 3-4 hours, and lasts ~6 hours. (26092297 (https://pubmed.ncbi.nlm.nih.gov/26092297/))

mechanism

- Droxidopa is basically an oral form of norepinephrine. It is taken up by neurons and metabolized into norepinephrine.
- The fact that droxidopa is taken up by neurons and subsequently secreted has unique benefits:
    - [1] The duration of action of droxidopa may last longer than its serum half-life.
    - [2] Droxidopa may support the *normal*, *synchronized* function of the sympathetic nervous system (rather than hitting any receptor in any tissue).

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ephedrine

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- ⚠️ Ephedrine is not supported by substantial evidence outside of short-term use in anesthesiology.
- ⚠️ Tachyphylaxis may result from the depletion of catecholamine stores.
- Contraindications include:
  - Drug interactions, including various antidepressants and MAO inhibitors.
  - Baseline tachycardia.
  - Angle-closure (narrow-angle) glaucoma.
  - Renal impairment.
  - Heart disease (including coronary artery disease, history of arrhythmia).

drug-drug interactions

- MAO inhibitors (may increase BP, impair ephedrine metabolism).
- Digoxin (may increase risk of arrhythmia).

side effects

- Agitation, insomnia, anxiety, restlessness.
- Tachycardia, hypertension, angina, arrhythmias.
- Nausea, vomiting.
- Urinary retention.

---

indications, advantages 👍

- ⚠️ There is minimal reason to ever use this drug in an ICU.
  - [1] If ephedrine causes a complication such as tachyarrhythmia or hypertension, it will take hours to wear off, so you'll be left managing this complication for a while. Standard, titratable ICU medications are safer and easier to use (e.g., norepinephrine infusion).
  - [2] Tachyphylaxis prevents ephedrine from being a useful agent to wean off IV vasopressors.
- Ephedrine could be used as a pressor agent when continuous infusion isn't possible.

---

dosing

- IV ephedrine: ~10 mg IV bolus, repeated q5-10 minutes. Don't exceed >150 mg total dose in 24 hours.
- IM ephedrine: 25-50 mg.
- PO ephedrine: Dosing for asthma: 12.5-25 mg PO q4hr PRN; don't exceed 150 mg daily.

---

pharmacology

- **Absorption**:
  - Oral administration:
    - Oral bioavailability is ~88%.
    - Maximal serum level is reached after ~2 hours.
  - IV administration.
  - IM administration: effects within ~10-20 minutes.
- **Distribution**:
  - Vd ~3 L/kg.
  - Protein binding is low (25%).
  - Lipid solubility allows crossing the blood-brain barrier.
- **Metabolism**:
  - Partial (~15%) hepatic metabolism yields an active metabolite, norephedrine (which is the drug phenylpropanolamine). The specific pathway isn't clear. Conversion to norephedrine seems to be saturable.
  - Minor metabolic pathways also include oxidative deamination to benzoic acid and 1,2-dihydroxypropylbenzene.
- **Elimination**:
  - Ephedrine (~70%) and norephedrine (~15%) are cleared by renal elimination.
- **Half-life & duration of action**:
  - Half-life is ~4-6 hours. However, acidic urine (pH <6) may accelerate excretion, reducing the half-life to 3 hours.

mechanism

- Ephedrine causes the activation of alpha- and beta-receptors (including beta-1 and beta-2 receptors) and stimulates the endogenous release of norepinephrine. The primary mechanism is inhibiting norepinephrine reuptake and displacing norepinephrine from storage vesicles. (Statler 2023) Ephedrine may also inhibit the action of MAO on norepinephrine. (Peck 2021)
- Physiological effects include:
  - Cardiac: Elevated cardiac output, heart rate, and blood pressure.
  - Respiratory: Bronchodilation; may stimulate the respiratory drive.

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peripheral pressors

(back to contents) (#top)

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peripheral IV line

- Hemodynamic stabilization should never wait until central access is obtained. Thus, peripheral vasopressors should be started immediately if the blood pressure or perfusion is inadequate.
- Norepinephrine is safe for short-term administration via a large peripheral vein. Ongoing peripheral infusion also appears safe, but it should ideally be performed within a well-designed protocol that includes frequent monitoring of the extremity and preparation for management of an extravasation reaction. (https://emcrit.org/emcrit/peripheral-vasopressors-extravasation/) Ongoing infusion should be *avoided* in deep ultrasound-guided peripheral IVs, where it may be impossible to monitor the tissue surrounding the end of the IV cannula.
  - Peripheral norepinephrine has been validated in a medical ICU using a rigorous protocol for IV line placement and close monitoring of their function. (26014852 (https://www.ncbi.nlm.nih.gov/pubmed/26014852))
- Phenylephrine and epinephrine have *not* been reported to cause tissue necrosis. Both agents have been administered subcutaneously *intentionally* in the past. Peripheral infusion of these agents appears generally safe (possibly safer than peripheral norepinephrine). (https://emcrit.org/pulmcrit/phenylephrine-epinephrine-central-access/)

- Vasopressin should arguably be avoided for peripheral administration because, if it extravasates, there is no vasodilatory agent to counteract its action.

midline catheter

- These are catheters placed in the arm, similar to a PICC, but shorter (typically 10-20 cm long, terminating before the shoulder).
- Clinician-placed midlines are evolving as an alternative to ultrasound-guided peripheral IVs or central lines.
- This is a rapidly emerging topic. Overall, vasopressor administration via midline catheters appears to be safe. (https://emcrit.org/emcrit/midlines-1/)

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just say no to dopamine

(back to contents) (#top)

- Mechanism/physiology
  - Dopamine hits a variety of receptors at different dose ranges ("dirty" drug).
  - It's often difficult to determine what it's doing to your patient. For example, low-dose dopamine can cause *hypotension* (due to a predominant effect of vasodilation), which can make it difficult to wean off the dopamine.
- Reasons dopamine should be abandoned:
  1. Dopamine increases mortality in RCTs: Dopamine increases mortality compared to norepinephrine in the subgroup of patients with cardiogenic shock. (20200382 (https://pubmed.ncbi.nlm.nih.gov/20200382/)) It also increased mortality compared to epinephrine among septic children. (26323041 (https://pubmed.ncbi.nlm.nih.gov/26323041/))
  2. It's often impossible to figure out what dopamine is doing (given the variety of different effects at different doses in different patients). This makes it impossible to titrate in any rational fashion (up-titration may cause dopamine to function entirely via a different mechanism).
  3. Dopamine has unique adverse endocrine effects.

4. Dopamine may directly stimulate diuresis via action on dopamine receptors, thereby falsely suggesting that renal perfusion is adequate.
5. There is a relatively high risk of tissue necrosis if it extravasates.
6. Better agents exist: there is nothing dopamine does that can't be achieved with the use of norepinephrine and/or epinephrine.
7. Dopamine may cause greater malperfusion of the gut compared to norepinephrine.

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fludrocortisone

(back to contents) (#top)

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contraindications, drug interactions, side effects 👎

contraindications

- Hypertension.
- Volume overload.

drug-drug interactions

- Antacids and PPIs: reduce enteral absorption.
- CYP enzyme inducers: increase clearance of fludrocortisone.

side effects

- Hypertension, congestive heart failure.
- Hypokalemia, hypomagnesemia, metabolic alkalosis.
- Doses >0.3 mg/day may start to cause glucocorticoid side effects (e.g., adrenal suppression, hyperglycemia).

---

indications, advantages 👍

- Adrenal insufficiency (e.g., Addison's disease).
- Salt-losing adrenogenital syndrome (congenital adrenal hyperplasia).
- Orthostatic hypotension and postural orthostatic tachycardia syndrome (POTS).
- Vasovagal syncope.

---

dosing

- General dosing concept:
  - Doses of 0.05-0.3 mg/d function primarily as a mineralocorticoid.
  - Doses >0.3 mg/day start to lose selectivity and exert corticosteroid effects (causing adrenal suppression). (28011746 (https://pubmed.ncbi.nlm.nih.gov/28011746/) , 32979782 (https://pubmed.ncbi.nlm.nih.gov/32979782/))
- Adrenal insufficiency (e.g., Addison's disease):
  - Usual dose is 0.1 mg daily.
  - The dosing range is 0.05-0.2 mg daily.
- Salt-losing adrenogenital syndrome: 0.1-0.2 mg daily.
- Orthostatic hypotension:
  - The dose starts at 0.1-0.2 mg/day.
  - Maximal dose is 1 mg/day, although efficacy may plateau above 0.5 mg/day.
- Septic shock:
  - It remains controversial whether fludrocortisone should be used in septic shock and, if it is used, what dose should be selected.
  - Recommended dose is generally 0.05 mg daily (based on the APROCCHSS trial). However, this is a rather low dose, making it dubious whether it would have any effect. One small pilot RCT suggested a nonsignificant trend towards reduced mortality with higher doses (0.1-0.2 mg daily). (39235623 (https://pubmed.ncbi.nlm.nih.gov/39235623/))

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pharmacology

- **Chemical properties**:

    - Molecular weight: 445 g/mol.
    - LogP: 1.4
- **Absorption**:
    - Rapidly and completely absorbed, but there is extensive first-pass metabolism, which results in low systemic bioavailability.
    - Cmax of 0.0012 – 0.2 ug/L with a Tmax of 0.5-2 hours (although absorption can be delayed in critical illness).
    - Factors affecting absorption:
        - High-fat meals can increase absorption.
        - Antacids or pH neutralization may decrease bioavailability.
- **Distribution**:
    - Protein binding is ~75% (mostly to albumin and corticosteroid-binding globulin).
    - Vd is ~80 L.
- **Metabolism**:
    - [1] Fludrocortisone acetate is an inactive prodrug requiring deacetylation by esterases in the liver. This yields an active alcohol form.
    - [2] Further metabolism occurs via reduction and conjugation pathways.
- **Elimination**:
    - Renal elimination, mostly as inactive metabolites.
- **Half-life & duration of action**:
    - Plasma half-life is ~3.5 hours.
    - Biological half-life is 18-36 hours.

mechanism of action

- [1] Binding to mineralocorticoid receptors. Mineralocorticoid receptors bound to aldosterone may be more resistant to proteolysis than mineralocorticoid receptors bound to cortisol. (38030548 (https://pubmed.ncbi.nlm.nih.gov/38030548/))
- [2] Fludrocortisone can potentiate the pressor effects of endogenous norepinephrine and angiotensin II via a noncanonical mechanism. (32979782 (https://pubmed.ncbi.nlm.nih.gov/32979782/))
    - Revealed by the observation that eplerenone acutely drops BP in some patients with dysautonomia. (26644241 (https://pubmed.ncbi.nlm.nih.gov/26644241/))

- This may involve stimulation of GPR30 (G protein-coupled receptor) or GPER-1 (G protein-coupled estrogen receptor-1). These receptors have high affinity for aldosterone but don't bind to cortisol. (38030548 (https://pubmed.ncbi.nlm.nih.gov/38030548/))

is fludrocortisone beneficial in septic shock?

- The APROCHSS trial used a combination of hydrocortisone and fludrocortisone. This has led some to question the value of adding fludrocortisone on top of hydrocortisone.
- Hydrocortisone 200 mg/day will provide plenty of stimulation of the mineralocorticoid receptor. However, there is still a biological rationale for why fludrocortisone could have activity beyond that of hydrocortisone (mentioned above and discussed in depth here: 38030548 (https://pubmed.ncbi.nlm.nih.gov/38030548/)).
- A recent pilot dose-finding study showed some weak signals of efficacy from fludrocortisone, but the overall effect was neutral. (39235623 (https://pubmed.ncbi.nlm.nih.gov/39235623/))
- My best guess is that hydrocortisone is the active ingredient in APROCHSS, and fludrocortisone wasn't having a significant effect. Nevertheless, this remains debated. Fludrocortisone is safe, so the addition of fludrocortisone is entirely reasonable.

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questions & discussion

(back to contents) (#top)

To keep this page small and fast, questions & discussion about this post can be found on another page ***here (shock)*** (https://emcrit.org/pulmcrit/shock/) and ***here (vasopressors)*** (https://emcrit.org/pulmcrit/pressors/)

Guide to emoji hyperlinks

- 🧮 = Link to online calculator.
- 💉 = Link to IBCC section about a drug.
- 📖 = Link to IBCC section covering that topic.
- 🌊 = Link to FOAMed site with related information.

- 📄 = Link to open-access journal article.
- 🎥 = Link to supplemental media.

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